IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Frans Janssens, Raymond Stokbroekx, Joseph Torremans and Marcel Luyckx

U.S. Patent No.: 4,219,559

Issued: August 26, 1980

For: N-HETEROCYCLYL-4-PIPERIDINAMINES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith is an Application for Extension of Patent Term under 35 U.S.C. 156 in the above-identified patent.

Please charge the $550.00 application fee to Deposit Account No. 10-750 in the name of Johnson & Johnson.

The Commissioner is hereby authorized to charge any additional fee which may be required or to credit any overpayments to Deposit Account 10-750.

A duplicate of this letter is enclosed.

Respectfully submitted,

N 10165 03/28/89 4219559 10-0750 010 111 550.00CH

David J. Levy
Registration No. 27,655
Attorney for Applicants

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933-7003
(201) 524-2821
February 10, 1989

EXPRESS MAIL # MB132880341
Date of Deposit - 2/10/89

JAB 286

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PATENT AND TRADEMARK OFFICE

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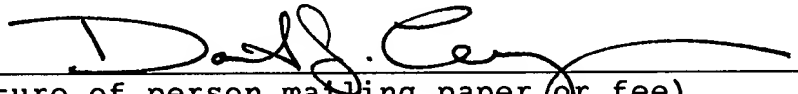
Certificate

"Express Mail" mailing number MB 132880341

Date of Deposit February 10, 1989

I hereby certify that this complete Application for Extension of Patent Term including the Transmittal Letter and all Exhibits and Attachments named therein is being deposited in duplicate with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patent and Trademarks, BOX PATENT EXT, Washington, D.C. 20231.

David J. Levy
(Typed or printed name of person mailing paper or fee)



(Signature of person mailing paper or fee)

E - Exam

JAB 286

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Frans Janssens, Raymond Stokbroekx, Joseph Torremans and Marcel Luyckx

U.S. Patent No.: 4,219,559

Issued: August 26, 1980

For: N-HETEROCYCLYL-4-PIPERIDINAMINES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Dear Sir:

Applicant Janssen Pharmaceutica N.V., a Belgiun business corporation represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,219,559 granted to Frans Janssens, Raymond Stokbroekx, Joseph Torremans and Marcel Luyckx on August 26, 1980 by virtue of an assignment to Janssen Pharmaceutica N.V. recorded in the United States Patent and Trademark Office on February 19, 1980 at reel 3733, frame 574.

Applicant hereby submits this Application for Extension of Patent Term under 35 U.S.C. 156 and provides the following information according to the relevant regulations set out at 37 C.F.R. 1.710 et seq. The numbering of the following paragraphs corresponds to the numbering of the requirements for an application set forth in 37 C.F.R. 1.740.

(1)

The approved product is the following:

Chemical Name:

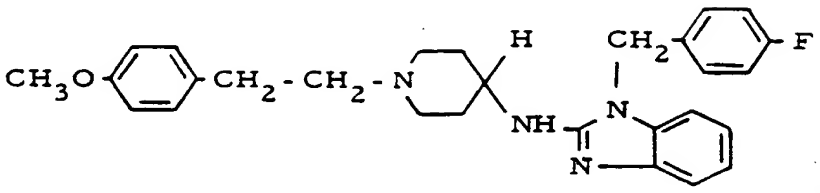
1-(4-fluorophenylmethyl)-N-[1-[2-(4-methoxyphenyl)-ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine

Generic Name:

astemizole

Manufacturer's Research Number:

R 43,512

Physical Structure: 

Characteristics:

- melting point 174-178° C
- molecular formula $C_{28}H_{31}FN_4O$

(2)

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. 355)

(3)

The approved product received permission for commercial marketing or use under Section 505 of the Federal Food Drug and Cosmetic Act (21 U.S.C. 355) on the following date:

December 29, 1988.

(4)

The approved product is a human drug product containing astemizole as the sole active ingredient. See paragraph (1) above for a more complete description of astemizole. Astemizole has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act.

(5)

This application for extension of patent term under 35 U.S.C. 156 is being submitted within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. 1.720(f). The last day on which this application could be submitted is February 27, 1989.

(6)

The complete identification of the patent for which this extension is being sought is as follows:

Inventors: Frans Janssens, Raymond Stokbroekx, Joseph Torremans and Marcel Luyckx

Patent Number: 4,219,559

Date of Issue: August 26, 1980

Date of Expiration: August 26, 1997

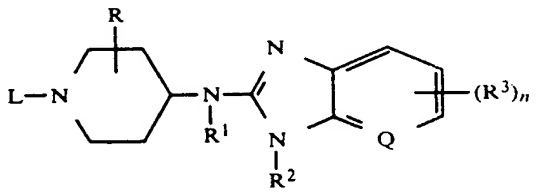
(7)

A copy of the patent for which an extension is being sought is appended hereto as Exhibit A.

(8)

The records of the undersigned do not indicate that any disclaimers, certificates of correction, receipts of maintenance fee payments or re-examination certificates were issued in the patent identified in paragraph (6). A letter dated April 28, 1981 was filed by Geoffrey G. Dellenbaugh, attorney for assignee in the file of the patent bringing certain printing errors to the attention of the Commissioner. A copy of this letter is appended hereto as Exhibit B.

United States Patent Number 4,219,559 claims the approved product as well as a method of using the approved product. Claims 1, 2, 6, 7, 11, 12, 17, 18 and 19 of U.S. Patent 4,219,559 each read on the approved product or a method of using the approved product. The following is a demonstration of the manner in which each of such patent claims reads on the approved product, it being noted that the "formula" to which reference is made in claims 1, 6, 11, 17, 18 and 19 is the following structure which is recited in all of such claims:



Claims 1, 6, 11, 17, 18 and 19:

- Choose R as "hydrogen";
- Choose R^1 as "hydrogen";
- Choose R^2 as "mono-...aryl (lower alkyl)";
- Choose the "aryl" of "mono-...aryl(lower alkyl)" as "substituted phenyl", see column 43, line 44;
- Choose "substituted phenyl" as "phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo", see column 43, lines 47-49;
- Choose n as the integer "0", thereby negating the need for choice of R^3;
- Choose Q as "CH";
- Choose L as "lower alkyl" which is substituted with one "aryl" substituent, see column 42, lines 64-68;
- Choose for the "aryl" substituent for L, "substituted phenyl", see column 43, line 44;

- Choose for the "substituted phenyl" as the "aryl" for the substitutent on "L", "a radical of the formula $R^6-C_pH_{2p}-O-$", see column 43, line 54; and
- Choose for the "$R^6-C_pH_{2p}-O-$" substituent of the "substituted phenyl" as a definition for "aryl" as a substituent on "L", p as "1" and R^6 as "hydrogen", see column 43, lines 54-57, thereby defining a methoxy group (CH_3-O-).

Claims 2, 7 and 12:

- Choose the free amine which is recited as "1-(4-fluorphenylmethyl)-N-[1-[2-(4-methoxyphenyl)-ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine".

The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review periods are as follows:

(a) The first Investigational New Drug (IND) application was filed April 22, 1980, was effective as of October 31, 1980 and was assigned IND # 17,431.

(b) The New Drug Application (NDA) was initially submitted on February 25, 1985 and was assigned NDA # 19-402.

(c) The NDA for the approved product was approved on December 29, 1988.

A brief description of the significant activities and dates applicable to such activities undertaken by the marketing applicant during the applicable regulatory review with respect to the approved product is appended hereto as Exhibit C. In this regard, it should be noted that the Applicant herein is Janssen Pharmaceutica N.V., a corporation of Belgium and a wholly-owned subsidiary of Johnson & Johnson, a corporation of New Jersey, U.S.A. While U.S. Patent 4,219,559 has been and is now owned by Janssen Pharmaceutica N.V., the IND and NDA submissions described herein were undertaken by Janssen Pharmaceutica, Inc., a New Jersey corporation which is a wholly-owned subsidiary of Johnson & Johnson, the Janssen Research Foundation, a Delaware corporation, which is a wholly-owned subsidiary of Johnson & Johnson and other entities which are directly or indirectly subsidiaries of Johnson & Johnson. All IND and NDA activities undertaken as described in Exhibit C have been carried out under license from Janssen Pharmaceutica N.V. and with the full and complete permission of Janssen Pharmaceutica N.V. and Johnson & Johnson.

Applicant is of the opinion that U.S. Patent 4,219,559 is eligible for extension under 35 U.S.C. 156.

The length of extension claimed in the present application is two years from August 26, 1997 to August 26, 1999. The requested two year extension is the maximum permitted by the limitations of 35 U.S.C. 156(g)(4)(C). The requested extension does not exceed the fourteen year maximum from the date of approval, i.e. to December 29, 2002, imposed by the limitation of 35 U.S.C. 156(c)(3). This extension is supported by the regulatory review period for the approved product, which exceeds two years.

(13)

The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in the present application for extension.

(14)

Accompanying this application is a transmittal letter which requests that the required fee for the present application for extension to be charged to Deposit Account Number 10-750.

(15)

The name, address, and telephone number of the person to who inquiries and correspondence relating to the present application for patent term extension are to be directed is as follows:

Address: Robert L. Minier
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933-7003

Telephone Calls: David J. Levy
(201) 524-2821

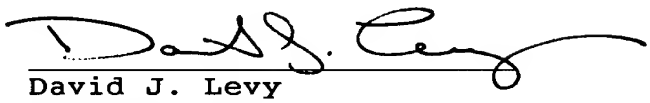
(16)

A duplicate of this application is enclosed. The required certification is appended hereto as Exhibit D.

(17)

The Declaration required by 37 C.F.R. 1.740(b) is attached hereto as Exhibit E.

Respectfully submitted,



David J. Levy
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Attorney for Applicant

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February 10, 1989

EXHIBIT A

United States Patent [19]

Janssens et al.

[11] **4,219,559**

[45] **Aug. 26, 1980**

[54] **N-HETEROCYCLYL-4-PIPERIDINAMINES**

[75] Inventors: **Frans Janssens**, Rijmenam; **Raymond Stokbroekx**; **Joseph Torremans**, both of Beerse; **Marcel Luyckx**, Geel, all of Belgium

[73] Assignee: **Janssen Pharmaceutica N.V.**, Beerse, Belgium

[21] Appl. No.: **2,276**

[22] Filed: **Jan. 10, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 892,534, Apr. 3, 1978, abandoned.

[51] **Int. Cl.**[2] **A61K 31/445**; C07D 401/04

[52] **U.S. Cl.** **424/267**; 424/256; 424/263; 424/248.51; 424/248.54; 424/248.55; 424/248.56; 546/118; 546/194; 546/199; 544/127; 544/139

[58] **Field of Search** 546/118, 194, 199; 544/127, 139; 424/248.51, 248.54, 248.55, 248.56, 256, 263, 267

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,963,727	6/1976	Ueno et al.	546/199
3,989,707	11/1976	Janssen et al.	546/199
4,002,623	1/1977	Kadin	546/199

Primary Examiner—John M. Ford
Assistant Examiner—Robert T. Bond
Attorney, Agent, or Firm—Geoffrey G. Dellenbaugh

[57] **ABSTRACT**

Novel N-heterocyclyl-4-piperidinamines wherein said heterocyclic radical is an optionally substituted 1H-benzimidazol-2-yl or 3H-imidazo[4,5-b]pyridin-2-yl radical, said compounds being useful as antihistaminic agents.

19 Claims, No Drawings

N-HETEROCYCLYL-4-PIPERIDINAMINES

CROSS-REFERENCE TO RELATED APPLICATIONS:

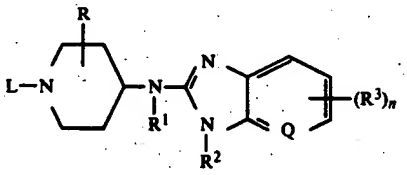
This is a continuation-in-part of our copending application Ser. No. 892,534, filed Apr. 3, 1978, now abandoned.

BACKGROUND OF THE INVENTION

In U.S. Pat. No. 2,971,005 there are described 2-(phenylmethylamino)benzimidazoles having local anaesthetic and antifibrillatory properties and in U.S. Pat. No. 2,857,391 there are described a number of 2-(aminomethyl)benzimidazoles. The compounds of this invention differ therefrom essentially by the nature of the 4-piperidinyl-group, attached to the amino nitrogen atom and by their unexpected antihistaminic properties. Also known in the art is 1-methyl-N-phenyl-N-phenylmethyl-4-piperidinamine, an antihistaminic compound which is generically designated as Bamipine (see the Merck index, 8th edition (1968) p. 118). The compounds of this invention are structurally different since they invariably contain a 1H-benzimidazol-2-yl or 3H-imidazo [4,5-b]pyridin-2-yl radical, attached to the amino nitrogen atom.

DESCRIPTION OF THE PREFERRED EMBODIMENTS:

This invention is concerned with a novel series of N-heterocyclyl-4-piperidinamines which may structurally be represented by the formula:



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and monoand diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula $Z—C_mH_{2m}—$, wherein

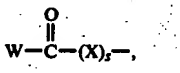
m is an integer of from 1 to 6 inclusive; and

Z is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-di-benzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula T-N(R^4)—, wherein

R^4 is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula



wherein

s is the integer 0 or 1;

X is a member selected from the group consisting of 0 and —N(R^5)—, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl-)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono-and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substitutents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6—C_pH_{2p}—O—$, wherein

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and a radical of the formula $R^7—O—$, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl;

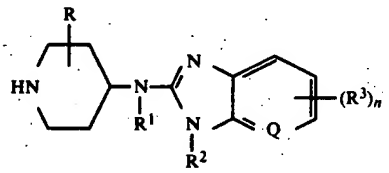
wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from

the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl wherein said aryl is as defined hereabove.

As used in the foregoing definitions the term "lower alkyl" is meant to include straight and branch chained hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; the term "alkyl" as used in the definition of R^2 includes straight and branch chained hydrocarbon radicals having from 1 to 10 carbon atoms, such as, for example, the above-indicated lower alkyls and higher homologs such as heptyl, octyl, nonyl and decyl; the term "lower alkenyl" refers to straight alkenyl radicals having from 3 to 6 carbon atoms wherein the unsaturation is preferably located at the β-position but may also be located at the γ, δ, or ϵ-position such as for example, 2-propenyl, 2-butenyl, 3-pentenyl, 2-hexenyl and the like; the term "cycloalkyl" refers to cyclic hydrocarbon radicals having from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the term "halo" is generic to fluoro, chloro, bromo and iodo.

The compounds of formula (I) can generally be derived from a starting material of the formula


(II)

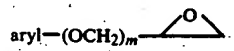
wherein R, R^1, R^2, R^3, n and Q are as previously defined by introducing the desired L-substituent onto the piperidine nitrogen by the application of art-known methods.

In general the introduction of said L into the intermediate (II) may conveniently be accomplished by the reaction of (II) with an appropriate reactive ester of the formula LY, (III), wherein L is as previously defined and Y is a reactive ester residue such as, for example, halo, preferably chloro or bromo, or a sulfonyloxy residue such as, for example, methylsulfonyloxy or 4-methylphenylsulfonyloxy and the like. The condensation reaction of (II) with (III) is conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene, and the like; a lower alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane and the like; N,N-dimethylformamide (DMF); nitrobenzene; and the like.

The additon of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, or an organic base such as, for example N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid that is liberated during the course of the reaction. In some circumstances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may be employed to enhance the rate of the reaction.

When L in formula (I) represents a(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl) lower alkyl radical it is appropriate to use a reactive ester (III) wherein the nitrogen atom in the 3-position of the of the 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl group is substituted with an appropriate protecting group, preferably a 1-methylethenyl group and removing said protecting group after completion of the condensation reaction. The removal of said protecting group may be accomplished by art-known procedures, such as acid hydrolysis when a 1-methylethenyl group is involved.

When L represents a 2-aryl-2-hydroxyethyl or a 3-aryloxy 2-hydroxypropyl radical, the introduction of said substituent into the intermediate (II) may conveniently be carried out by reacting (II) at an elevated temperature with an appropriate oxirane of the formula


(IV)

wherein m is 0 or 1.

The reaction of (II) with (IV) may be carried out in an appropriate organic solvent or, optionally, in the absence of any solvent. Suitable solvents which may be employed include, for example, aromatic hydrocarbons such as benzene, methylbenzene, dimethylbenzene and the like; halogenated hydrocarbons such as, for example, trichloromethane, dichloromethane and the like; lower alkanols such as, methanol, ethanol, 2-propanol and the like alcohols; and mixtures of such solvents. When the piperidine derivative (II) is in the form of an acid addition salt it is appropriate to add to the reaction mixture an appropriate base such as, for example, sodium carbonate in order to liberate the free acid from the salt.

The compounds of formula (I) wherein L represents a 2-hydroxyethyl radical may be prepared by the reaction of an appropriate piperidine of formula (II) with oxirane, following the same procedure as described for the reaction of (IV) with (II).

When L is, at the point of attachment to the piperidine nitrogen atom, a primary or secondary alkyl group, the compounds (I) may also be prepared by the reductive amination of an aldehyde or ketone corresponding with the alcohol L—OH with a piperidine derivative of formula (II) following art-known procedures. In a convenient method of operation a mixture of the aldehyde or ketone and (II) in an appropriate organic solvent is hydrogenated in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal.

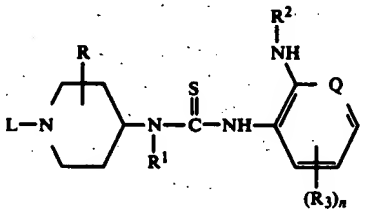
Appropriate organic solvents include lower alkanols, such as, for example, methanol, ethanol, propanol and the like. The rate of the hydrogenation reaction may be enhanced by carrying out said reaction in the presence of an appropriate weak acid such as, for example, acetic acid. When the piperidine derivative (II) is in the form of an addition salt with a strong acid, e.g., hydrochloric or hydrobromic acid it is appropriate to add thereto a salt of a strong base with a weak acid., e.g., sodium acetate to bind said strong acid. When (II) contains groups that are themselves susceptable to catalytic hydrogenation, e.g. when R^2 represents a arylmethyl group, it may be appropriate to add to the reaction mixture an appropriate catalyst poison, such as, for example, thiophene.

When L represents a radical of formula $Z—C_mH_{2m}—$, wherein m is an integer of from 2 to 6 inclusive and wherein Z is as previously defined, the compounds of formula (I) can also be prepared by the reaction of (II) with an appropriate alkenyl derivative,

$Z—C_mH_{2m-1}$, according to art-known methods of carrying out similar addition- reactions, e.g., by stirring and heating the reactants together in and appropriate reaction-inert organic solvent such as, for example, a lower alkanol such as 2-propanol, butanol and the like.

When L represents a 2-(aroylamino)ethyl radical or a 2-arylethyl radical the compounds (I) can also be obtained by the reaction of (II) with an appropriate I-aroylaziridine or an appropriate ethenylarene, respectively. Said reactions are preferably carried out in an appropriate reaction-inert organic solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol, propanol, butanol and the like alcohols; an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; a ketone, e.g., 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane and the like; N,N-dimethylformamide; nitrobenzene; and the like; or a mixture of such solvents. Elevated temperatures are appropriate in order to enhance the rate of the reaction and preferably the reaction is carried out at the reflux temperature of the reaction mixture.

The compounds of formula (I) can also be prepared by the cyclodesulfurization of an appropriate thiourea derivative of the formula



(V)

Said cyclodesulfurization reaction may be carried out by the reaction of (V) with an appropriate alkyl halide, preferably iodomethane in an appropriate reaction-inert organic solvent, e.g., a lower alkanol such as methanol, ethanol, 2-propanol and the like. Otherwise, the cyclodesulfurization reaction may be carried out by the reaction of (V) with an appropriate metal oxide or salt in an appropriate solvent according to the procedure described, for example, in Pharmazie, 31, 348 (1976). For example, the compounds of formula (I) can easily be prepared by the reaction of (V) with an appropriate Hg(II) or Pb(II) oxide or salt, such as, for example HgO, $HgCl_2$, $Hg(OAc)_2$, PbO or $Pb(OAc)_2$. In certain instances it may be appropriate to supplement the reaction mixture with a small amount of sulfur. Even so methanediimines, especially N,N'-methanetetraylbis[-cyclohexanamine], may be used as cyclodesulfurizing agents. Suitable reaction-inert organic solvents that may advantageously be employed include lower alkanols, e.g., methanol, ethanol, 2-propanol and the like; halogenated hydrocarbons, e.g., dichloromethane and trichloromethane; ethers, e.g. tetrahydrofuran, 2,2'-oxybispropane and the like; and mixture of such solvents.

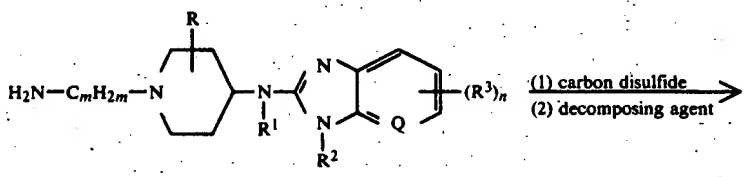
The compounds of formula (I) wherein R^2 is other than hydrogen, said R^2 being represented by R^2 and said compounds by the formula (I-a), can also be prepared starting from a corresponding compound (I) wherein R^2 is hydrogen, (I-b), by introducing said R^2 according to art-known procedures as previously described herein for the introduction of L into starting materials of formula (II). In a preferred method of operation (I-b) is reacted with an appropriate reactive ester R^2 Y, (VI), wherein R^2 and Y are as previously defined. The reaction is carried out under similar conditions as previously described herein for the reaction of (II) with (III). Since the compounds of formula (I-b) are somewhat less reactive it is advantageous to conduct the alkylation reaction in the presence of a small amount of a strong metal base such as, for example, sodium hydride.

The compounds of formula (I) wherein R^1 and R^2 are both different from hydrogen, said R^1 being represented by R^1 and said R^2 by R^2_a can also be derived from the corresponding compounds wherein R^1 is hydrogen by introducing the R^1_a-group in a similar manner as described hereinabove for the preparation of compound (I-b) starting from (I-a).

Following the procedure, described hereinabove for the preparation of compounds (I) starting from (V), the compounds of formula (I), wherein L represents a (1H-benzimidazol-2-ylamino)lower alkyl radical or a 1-(aryllower alkyl)-1H-benzimidazol-2-ylamino)lower alkyl radical (I-c), may even so be derived from the corresponding isothiocyanates (VII) by subjecting the latter to an addition-reaction with a benzenediamine (VIII) and subsequently cyclodesulfurizing the intermediately formed thiourea (IX).

The isothiocyanates (VII) may be prepared following art-known procedures for the preparation of isothiocyanates [see, for example, Saul Patal Ed. "The Chemistry of Cyanates and their Thioderivatives" John Wiley & Sons—Chichester—New York—Brisbane—Toronto (1977) p. 1013–1053], such as, for example by reacting the corresponding amine (VI) with carbon disulfide, preferably in the presence of alkali e.g., sodium hydroxide and the like, and decomposing the intermediately formed dithiocarbamate with for example N,N'-methanetetraylbis[cyclohexanamine], a lower alkyl chloroformate or another appropriate decomposing agent as known in the art.

The foregoing reactions are illustrated as follows:



(VI)

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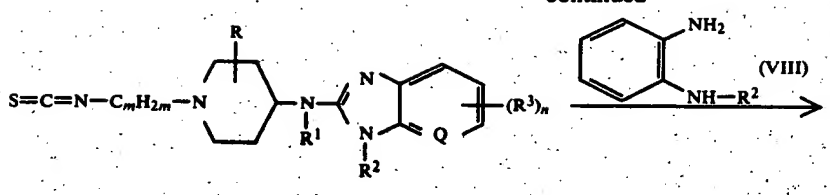
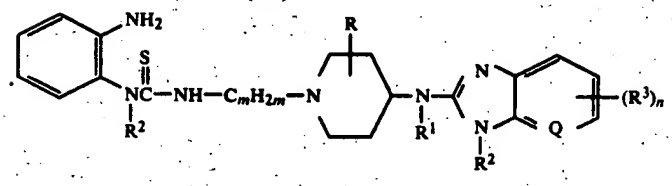
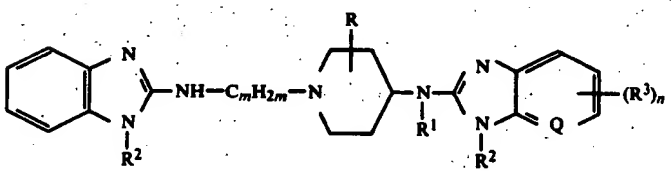


(VII)



(IX)

cyclodesulfurization



(I-c)

The compounds of formula (I) wherein L represents a radical $Z—C_mH_{2m}—$, wherein Z represents a radical of the formula $W—CO—(X)_s—$, wherein s is 1, X is O and W is an optionally substituted amine, a 1-pyrrolidinyl, a 4-morpholinyl or a 1-piperidinyl radical, said compounds being represented by the formula (I-d), may be prepared by the reaction of the corresponding amine, pyrrolidine, morpholine or piperidine with an appropriate N-[1-(halolower alkyl)-4-piperidinyl]-1H-benzimidazol-2-amine in the presence of an appropriate carbonate, e.g. sodium carbonate and the like.

Compounds of formula (I) which contain at least one hydroxyl-group as a substituent can conveniently be derived from the corresponding phenylmethoxy substituted compounds by subjecting the latter to a catalytic hydrogenation in the presence of an appropriate catalyst, e.g., palladium-on-charcoal and the like. These hydroxyl-derivatives may even so be derived from the corresponding lower alkyloxy substituted analogs by hydrolyzing the latter in acidic medium, using for example hydrogen bromide in acetic acid. The hydroxyl-substituted compounds may in turn be O-alkylated or acylated by reacting the latter with a halide, an alkanoyl halide, an alkyloxycarbonyl halide, an isocyanate and the like. The hydroxyl-substituted compounds may also be converted into halides by reacting therewith a suitable halogenating agent, e.g. thionyl chloride, phosphor pentabromide and the like in the presence of an appropriate solvent, e.g., a trichloromethane and the like.

Amino-substituted compounds may, for example, be derived from the corresponding nitro- and cyano-substituted compounds by reducing the latter, e.g., by catalytic hydrogenation in the presence of an appropriate catalyst, such as, for example, Raney-nickel and the like. The amino-substituted compounds may in turn be N-alkylated or acylated by the reaction thereof with an appropriate alkylating agent or acylating agent, e.g., a halide, an alkanoyl halide, an alkoxycarbonyl halide, an isocyanate and the like.

Secondary and tertiary amino-substituted compounds of formula (I) may be prepared by substituting, for example, an appropriate halo-substituted compound with the desired primary or secondary amine.

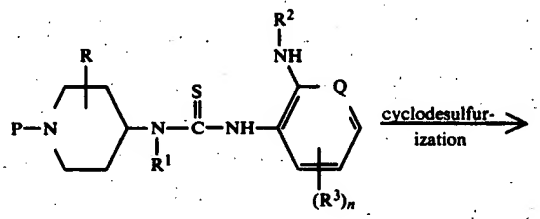
Aminocarbonyl-substituted compounds may conveniently be derived from the corresponding esters by reacting the latter with ammonia or an appropriate primary-or a secondary amine in a suitable solvent.

Compounds of formula (I) which contain in their structure a sulfonyl group may easily be derived from the corresponding thio compounds by oxidizing the latter with an appropriate oxydizing agent, e.g. hydrogen peroxide and the like.

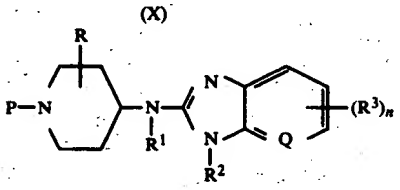
In all of the foregoing and in the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

The compounds of formula (I) may be converted to the therapeutically active non-toxic acid addition salt form by treatment with an appropriate acid, such as, for example, an inorganic acid, such as hydrohalic acid, e.g., hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or an organic acid, such as, for example, acetic, propanoic, 2-hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, benzoic, 3-phenyl-2-propenoic, α-hydroxybenzeneacetic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The starting materials of formula (II) herein can generally be prepared starting from a thiourea derivative of the formula (X) wherein R, R^1, R^2, R^3 and n are as previously defined and P is an appropriate protecting group such as, for example, lower alkyloxycarbonyl or phenylmethoxycarbonyl, by subjecting (X) to a cyclodesulfurization reaction to obtain an intermediate of the formula (XI) and thereafter eliminating the protecting group in the usual manner.



(X)

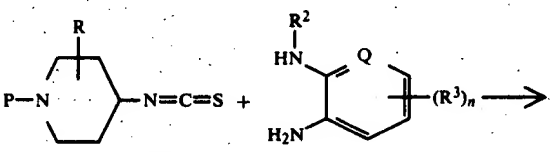


(XI)

(II)

The cyclodesulfurization of (X) to obtain (XI) can be carried out in the same manner as previously described herein for the preparation of the compounds (I) starting from (V). In order to remove the protecting group P there may be used art-known procedures. For example, when said group is a lower alkyloxycarbonyl group it may be removed by alkaline or preferably acid hydrolysis, using for example, hydrobromic acid in glacial acetic acid, and when said protecting group is a phenylmethoxycarbonyl group it may be removed by alkaline or acid hydrolysis or by catalytic hydrogenation using an appropriate catalyst such as palladium-on-charcoal. Intermediates of formula (XI) wherein R^2 is other than hydrogen can also be derived from the corresponding (XI) wherein R^2 is hydrogen by introducing the desired R^2-substituent according to art-known methodologies as described hereinabove in connection with the preparation of compounds (I-a) starting from (I-b).

The thiourea derivatives of formula (X) wherein R^1 represents hydrogen, (X-a), can be prepared by the reaction of an appropriate 4-isothiocyanatopiperidine of formula (XII) with an appropriate benzenediamine or pyridinediamine of formula (XIII), e.g., by simply stirring the reactants together in an appropriate organic solvent such as, for example, a lower alkanol, e.g. methanol, ethanol, 2-propanol and the like.



(XII) (XIII)

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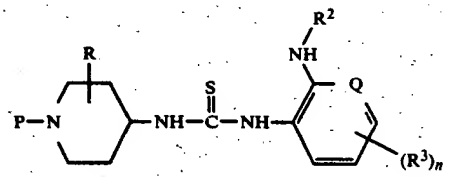
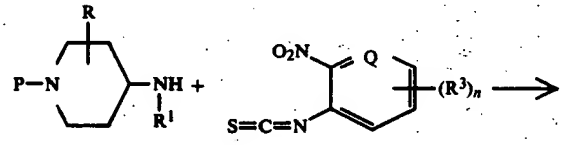
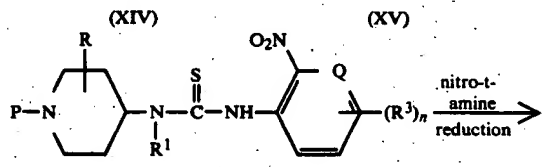


(X-a)

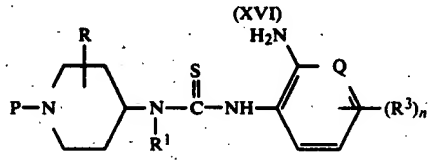
Thiourea derivatives of formula (X) wherein R^1 is as previously defined and R^2 is hydrogen, (X-b),), can be prepared by the reaction of an appropriate-4-piperidinamine of the formula (XIV) with an appropriate 1-isothiocyanato-2-nitrobenzene of the formula (XV), followed by the reduction of the nitro group of the thus obtained compound (XVI) following well-known nitro-to-amine reduction procedures such as for example by the reaction of (XVI) with nascent hydrogen or by catalytic hydrogenation using an appropriate catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like, or in the presence of more than one of such catalysts.



(XIV) (XV)



(XVI)



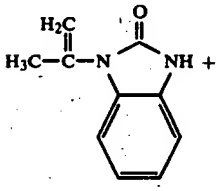
(X-b)

The precursor materials of formula (XIV) herein may be prepared following methods known in the art, e.g., by the reductive amination of the corresponding 4-piperidinone. The 4-isothiocyanatopiperidines of formula (XII) may in turn be prepared starting from the corresponding (XIV) wherein R^1 is hydrogen according to standard methods of preparing isothiocyanates starting from primary amines, e.g., by the reaction of the amine with carbon disulfide in alkaline medium and subsequent addition to the reaction mixture of an appropriate lower alkylcarbonochloridate.

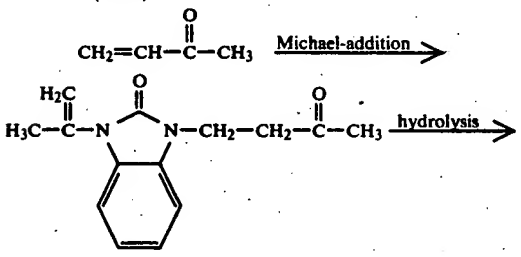
The starting materials of formula (XII) wherein P represents a lower alkyloxycarbonyl or phenylmethoxycarbonyl group can also be prepared by the reaction of a corresponding starting material (XII) wherein said P represents phenylmethyl by reacting the latter with an appropriate carbonochloridate.

The starting materials of formula (V) can be prepared using similar procedures as described hereinabove for the preparation of the thiourea derivatives of formula (X) starting however from an appropriate 4-piperidinone or 4-piperidinamine wherein the L-substituent is already present on the piperidine nitrogen atom.

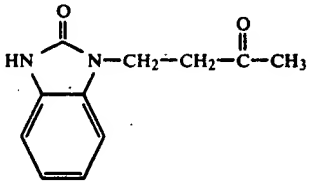
The ultimate starting materials in each of the foregoing preparations are known compounds or they may be prepared by the application of methodologies known in the art for preparing similar known compounds. The preparation of 4-(haloalkyl)-2H-1,4-benzoxazin-3(4H)-ones, for example, by the N-substitution-reaction of 2H-1,4-benzoxazin-3(4H)-one with a dihalolower alkyl group, is described in Belg. Pat. No. 859,415. 1,3-dihydro-1-(3-oxobutyl)-2H-benzimidazol-2-one (XIX) can be prepared by subjecting 1,3-dihydro-1-(1-methylethenyl)-2H-benzimidazol-2-one (XVII) and 3-buten-2-one to a Michael-addition procedure in the presence of a base such as, N,N-diethylethanamine and the like, and subsequently hydrolying the 1,3-dihydro-1-(1-methylethenyl)-3-(3-oxobutyl)-2H-benzimidazol-2-one (XVIII).



(XVII)



(XVIII)



(XIX)

The intermediates of the formulae (II) and (XI) are deemed to be novel and in view of their utility as starting materials in the preparation of the pharmaceutically active compounds of formula (I) they constitute an additional feature of this invention.

The compounds of formula (I) and their pharmaceutically acceptable acid addition salts are potent antihistaminic agents and as such they can be used to prepare valuable medicaments for human and animal therapy. The useful antihistaminic proterties of the compounds of formula (I) were demonstrated in the following test-procedure.

PROTECTION OF RATS FROM COMPOUND 48/80-INDUCED LETHALITY.

Compound 48/80, a mixture of oligomers obtained by condensation of p-methoxy-N-methyl-phenethylamine and formaldehyde has been described as a potent histamine releasing agent (Int. Arch. Allergy, 13, 336 (1958)). The protection from compound 48/80-induced lethal circulatory collapse appears to be a simple way of evaluating quantitatively the antihistaminic activity of test-compounds. Male rats of an inbred Wistar strain, weighing 240–260 g were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temp. $=21\pm1°$ C., relative humidity $=65\pm5\%$). The rats were treated subcutaneously or orally with a test compound or with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 ml/100 g of body weight). In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80 not more than 2.8% of the animals survived after 4 hours. Survival after 4 hours is therefore considered to be a safe criterion of a protective effect of drug administration. The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof were found very active in the above test, protecting the animals against compound 48/80-induced lethality at oral and subcutaneous doses not higher than 2.5 mg/kg. A number of the subject compounds were found effective even at doses as low as 0.16 mg/kg.

In view of their useful antihistaminic activity, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, an effective antihistaminic amount of the particular compound, in base or acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Acid addition salt of (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The following examples are intended to illustrate and not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

A. PREPARATION OF INTERMEDIATES:

EXAMPLE I

A mixture of 102 parts of ethyl 4-oxo-1-piperidinecarboxylate, 50 parts of methanamine and 400 parts of methanol is hydrogenated at normal pressure and at room temperature with 5 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated, yielding 111 parts of ethyl 4-(methylamino)-1-piperidinecarboxylate as a residue.

To a stirred and cooled mixture of 4 parts of sodium hydroxide in 60 parts of water are added successively 7.9 parts of carbon disulfide and 17.2 parts of ethyl 4-amino-1-piperidinecarboxylate at a temperature below 10° C. Stirring is continued for 30 minutes at this temperature. Then there are added dropwise 10.9 parts of ethyl carbonochloridate (exothermic reaction: temp. rises to about 35° C.). Upon completion, stirring is continued for 2 hours at 60° C. The reaction mixture is cooled and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated, yielding 22 parts (100%) of ethyl 4-isothiocyanato-1-piperidinecarboxylate as a residue.

By repeating the procedure of the second step there are also prepared starting from an appropriate amine:
4-isothiocyanato-1-(phenylmethyl)piperidine; and
1-[4,4-bis(4-fluorophenyl)butyl]-4-isothiocyanatopiperidine; mp. 92° C.

EXAMPLE II

To a stirred solution of 28.4 parts of 4-isothiocyanato-1-(phenylmethyl)piperidine in 315 parts of methylbenzene are added dropwise 41 parts of (phenylmethyl) carbonochloridate at room temperature. Upon completion, the whole is heated to reflux and stirring is continued overnight at reflux temperature. The reaction mixture is cooled and the solvent is evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 32 parts (97%) of (phenylmethyl) 4-isothiocyanato-1-piperidinecarboxylate as a residue.

EXAMPLE III

A mixture of 9.7 parts of 4-fluorobenzenemethanamine hydrochloride, 9.4 parts of 2-chloro-3-nitropyridine, 10.6 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred for 1 hour at 90° C. The reaction mixture is cooled and poured onto water. The precipitated product is filtered off and crystallized from 2-propanol, yielding 10.5 parts (71%) of N-(4-fluorophenylmethyl)-3-nitro-2-pyridinamine; mp. 76° C.

A mixture of 10.5 parts of N-(4-fluorophenylmethyl)-3-nitro-2-pyridinamine and 200 parts of methanol is hydrogenated at normal pressure and at room temperature with 2 parts of Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated, yielding 9.3 parts (100%) of N^2-(4-fluorophenylmethyl)-2,3-pyridinediamine as a residue.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:
N^1-(phenylmethyl)-4-(trifluoromethyl)-1,2-benzenediamine; and
4-chloro-N^1-(4-fluorophenylmethyl)-1,2-benzenediamine.

EXAMPLE IV

A mixture of 34.8 parts of 1,3-dihydro-1-(1-methylethenyl)-2H-benzimidazol-2-one, 28 parts of 3-buten-2-one, 20.2 parts of N,N-diethylethanamine and 270 parts of tetrahydrofuran is stirred and refluxed over week-end. The reaction mixture is evaporated, yielding 48.8 parts (100%) of 1,3-dihydro-1-(1-methylethenyl)-3-(3-oxobutyl)-2H-benzimidazol-2-one as a residue.

A mixture of 48.8 parts of 1,3-dihydro-1-(1-methylethenyl)-3-(3-oxobutyl)-2H-benzimidazol-2-one, 12 parts of 2-propanol, saturated with gaseous hydrogen chloride and 240 parts of 2-propanol is stirred for 3 hours at room temperature. The precipitated product is filtered off, washed with 2,2'-oxybispropane and dried, yielding 30 parts (73.4%) of 1,3-dihydro-1-(3-oxobutyl)-2H-benzimidazol-2-one.

EXAMPLE V

To a stirred mixture of 9 parts of 2H-1,4-benzoxazin-3(4H)-one, 0.9 parts of N,N,N-triethylbenzenemethanaminium chloride, 9 parts of sodium hydroxide solution 50% and 24 parts of water are added 10.4 parts of 1-bromo-3-chloropropane at 30° C. The whole is heated to 90° C. and stirring is continued for 3 hours at this temperature. The reaction mixture is cooled to about 70° C., methylbenzene is added and the whole is stirred overnight at room temperature. The organic phase is separated, dried, filtered and evaporated, yielding 10 parts of 4-(3-chloropropyl)-2H-1,4-benzoxazin-3(4H)-one as a residue.

EXAMPLE VI

A mixture of 10.6 parts of ethyl 4-isothiocyanato-1-piperidinecarboxylate, 11.6 parts of 4-chloro-N^1-(phenylmethyl)-1,2-benzenediamine and 90 parts of tetrahydrofuran is stirred overnight at room temperature. The reaction mixture is evaporated, yielding 21 parts (100%) of ethyl 4-[{[{5-chloro-2-[(phenylmethyl-)amino]phenyl}amino]thioxomethyl}amino]-1-piperidinecarboxylate; mp. 162° C.

EXAMPLE VII

Following the procedure of Example VI and using equivalent amounts of the appropriate starting materials there are prepared:
ethyl 4-{[(2-amino-5-chlorophenyl)aminothioxomethyl-]amino}-1-piperidinecarboxylate; mp. 162.2° C.;
ethyl 4-{[(2-aminophenyl)aminothioxomethyl]amino}-1-piperidinecarboxylate as a residue;

ethyl 4-{[(2-amino-5-methylphenyl)aminothioxomethyl]amino}-1-piperidinecarboxylate as a residue;
ethyl 4-[{[{2-[(phenylmethyl)amino]-3-pyridinyl}amino]thioxomethyl}amino]-1-piperidinecarboxylate; mp. 146.7° C.;
ethyl 4-{[{2-[(phenylmethyl)amino]-5-(trifluoromethyl)phenyl}amino]thioxomethylamino}-1-piperidinecarboxylate as a residue;
ethyl 4-[{[(2-amino-4-fluorophenyl)amino]thioxomethyl}amino]-1-piperidinecarboxylate as a residue;
ethyl 4-[{[{5-chloro-2-[(4-fluorophenylmethyl)amino]-phenyl}amino]thioxomethyl}amino]-1-piperidineearboxylate as a residue;
(phenylmethyl) 4-[{2-[(4-fluorophenylmethyl)amino]-3-pyridinylamino}thioxomethylamino]-1-piperidinecarboxylate;
N-(2-nitrophenyl)-N'-[1-(2-phenylethyl)-4-piperidinyl]-N'-(phenylmethyl)thiourea; mp. 151.1° C.;
N-{1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl}-N'-phenylthiourea; mp. 90° C.;
ethyl 4-[{[(2-amino-3-pyridinyl)amino]thioxomethyl}-amino]-1-piperidinecarboxylate; mp. 176.9° C.;
4-[{[(2-phenylamino)phenyl]aminothioxomethyl}-amino]-1-piperidinecarboxylate; mp. 154.2° C.; and
ethyl 4-[{[{2-(4-fluorophenylamino)phenyl]amino}thioxomethyl]-amino}-1-piperidinecarboxylate as a residue.

EXAMPLE VIII

A mixture of 21.6 parts of 1-isothiocyanato-2-nitrobenzene and 45 parts of tetrahydrofuran is stirred till all solid enters solution. Then there are added 29.5 parts of N-(1-methylethyl)-1-(2-phenylethyl)-4-piperidinamine and 160 parts of ethanol and the whole is stirred overnight at room temperature. The reaction mixture is evaporated and the residue is crystallized from 2-propanol. The product is filtered off and dried, yielding 43 parts (84%) of N-(1-methylethyl)-N'-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]thiourea; mp. 100.6° C.

EXAMPLE IX

Following the procedure of Example VIII the following thiourea derivatives are prepared by the reaction of an appropriate 4-piperidinamine with an appropriate 1-isothiocyanato-2-nitrobenzene.
ethyl 4-[methyl-{[(2-nitrophenyl)amino]thioxomethyl}-amino]-1-piperidinecarboxylate;
ethyl 4-{butyl[(2-nitrophenyl)aminothioxomethyl-]amino}-1-piperidinecarboxylate as a residue;
N-ethyl-N'-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-thiourea;
N-(2-nitrophenyl)-N'-[1-(2-phenylethyl)-4-piperidinyl]-N'-propylthiourea; mp. 90.3° C.;
N-cyclopropyl-N'-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]thiourea; mp. 150.1° C.; and
cis+trans-methyl 3-methyl-4-[{[(2-nitrophenyl)amino]-thioxomethyl}amino]-1-piperidinecarboxylate; mp. 157.5° C.

EXAMPLE X

A mixture of 43 parts of N-(1-methylethyl)-N'-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]thiourea and 800 parts of methanol, saturated with ammonia is hydrogenated at normal pressure and at room temperature with 6 parts of palladium-on-charcoal catalyst 10% and 6 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen is taken up, the catalysts are filtered off over Hyflo and the filtrate is evaporated, yielding 39 parts (100%) of N-(2-aminophenyl)-N'-(1-methylethyl)-N'-[1-(2-phenylethyl)-4-piperidinyl]thiourea as a residue.

EXAMPLE XI

Following the procedure of Example X and using an equivalent amount of an appropriate nitro-compound as a starting material, there are prepared:
ethyl 4-[{[(2-aminophenyl)amino]thioxomethyl}methylamino]-1-piperidinecarboxylate;
ethyl 4-{[(2-aminophenyl)aminothioxomethyl]-butylamino}-1-piperidinecarboxylate;
N-(2-aminophenyl)-N'-[1-(2-phenylethyl)-4-piperidinyl]thiourea;
N-(2-aminophenyl)-N'-[1-(2-phenylethyl)-4-piperidinyl]-N'-propylthiourea;
N-(2-aminophenyl)-N'-cyclopropyl-N'-[1-(2-phenylethyl)-4-piperidinyl]thiourea;
methyl 4-{[(2-aminophenyl)amino]thioxomethylamino}-3-methyl-1-piperidinecarboxylate;
N-(2-aminophenyl)-N'-[1-(2-phenylethyl)-4-piperidinyl]-N'-(phenylmethyl)thiourea as a residue.

EXAMPLE XII

A mixture of 23 parts of (phenylmethyl) 4-[{2-[(4-fluorophenylmethyl)amino]-3-pyridinylamino}thioxomethylamino]-1-piperidinecarboxylate, 17 parts of mercury oxide, 0.1 parts of sulfur and 450 parts of tetrahydrofuran is stirred and refluxed for 1 hour. The reaction mixture is filtered over Hyflo and the filtrate is evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 20 parts (93%) of (phenylmethyl) 4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinecarboxylate; mp. 130° C.

EXAMPLE XIII

Following the procedure of Example XII and using equivalent amounts of the appropriate starting materials there are prepared:
ethyl 4-[(1H-benzimidazol-2-yl)methylamino]-1-piperidinecarboxylate;
ethyl 4-[(1H-benzimidazol-2-yl)butylamino]-1-piperidinecarboxylate; mp. 225.9° C.
ethyl 4-[1-(phenylmethyl)-5-(trifluoromethyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 200° C.;
ethyl 4-(5-fluoro-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 227.5° C.;
ethyl 4-[5-chloro-1-(phenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 211.9° C.;
ethyl 4-[3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinecarboxylate; mp. 148.6° C.;
ethyl 4-[5-chloro-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 215.8° C.;
methyl 4-(1H-benzimidazol-2-ylamino)-3-methyl-1-piperidinecarboxylate; mp. 155° C.;
ethyl 4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinecarboxylate; mp. 134.4° C.;
ethyl 4-[(3-imidazo[4,5-b]pyridin-2-yl)amino]-1-piperidinecarboxylate; mp. 216.1° C.;
ethyl 4-(1-phenyl-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 137° C.; and

ethyl 4-[1-(4-fluorophenyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 153° C.

EXAMPLE XIV

A mixture of 28 parts of ethyl 4-{[(2-aminophenyl-)aminothioxomethyl]amino}-1-piperidinecarboxylate, 112 parts of iodomethane and 240 parts of ethanol is stirred and refluxed for 8 hours. The reaction mixture is evaporated and the residue is taken up in water. The whole is alkalized with ammonium hydroxide and the product is extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanol and 2,2'-oxybispropane. The product is filtered off and dried, yielding 7 parts (28%) of ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

ethyl 4-(5-chloro-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 234.1° C.; and

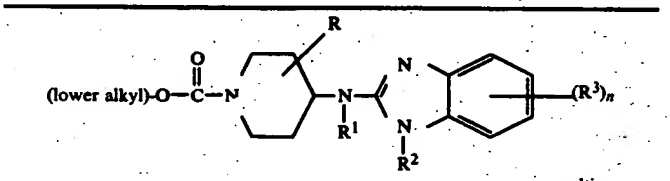
ethyl 4-(5-methyl-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate.

EXAMPLE XV

A mixture of 19 parts of methyl 4-(1H-benzimidazol-2-ylamino)-3-methyl-1-piperidinecarboxylate, 11 parts of 1-(chloromethyl)-4-fluorobenzene, 6 parts of sodium carbonate and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70° C. The reaction mixture is cooled and poured onto water. The product is extracted three times with methylbenzene. The combined extracts are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 8 parts (38%) of methyl 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-3-methyl-1-piperidinecarboxylate; mp. 172.5° C.

EXAMPLE XVI

Following the procedure of Example (XIII) the following 4-(1-R^2-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylates are prepared by alkylating the corresponding 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate with an appropriate chloride, bromide or iodide of the formula R^2X:



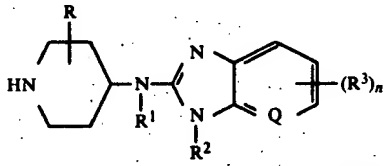
lower alkyl	R	R^1	R^2	$(R^3)_n$	melting point
C_2H_5	H	H	CH_3	H	166.7° C.
C_2H_5	H	H	CH_3	5(6)-CH_3	142.0° C.
C_2H_5	H	H	C_2H_5	H	—
C_2H_5	H	H	n. C_3H_7	H	—
C_2H_5	H	H	i. C_3H_7	H	—
C_2H_5	H	H	n. C_4H_9	H	—
C_2H_5	H	H	n. C_5H_{11}	H	—
C_2H_5	H	H	n. C_6H_{13}	H	—
C_2H_5	H	H	n. C_7H_{15}	H	—
C_2H_5	H	H		H	—
C_2H_5	H	H	4-Br—C_6H_4—CH_2	H	—
C_2H_5	H	H	C_6H_5—CH_2	5(6)-CH_3	179.3° C.
C_2H_5	H	H	C_6H_5—CH_2	H	—
C_2H_5	H	H	4-CH_3—C_6H_4—CH_2	H	177.7° C.
C_2H_5	H	H	4-F—C_6H_4—CH_2	H	—
C_2H_5	H	H	2-F—C_6H_4—CH_2	H	176.0° C.
C_2H_5	H	H	4-F—C_6H_4—CH_2	5(6)-F	182.5° C.
C_2H_5	H	H	C_6H_5—CH_2	5(6)-F	184.0° C.
CH_3	CH_3	H	C_6H_5—CH_2	H	191.0° C. (cis + trans-isomer)
C_2H_5	H	H	4-NO_2—C_6H_4—CH_2	H	—
C_2H_5	H	CH_3	C_6H_5—CH_2	H	258.0° C.(HCl-salt)
C_2H_5	H	H	4-F-2—CH_3—C_6H_3—CH_2	H	—

EXAMPLE XVII

A mixture of 7 parts of ethyl 4-{[5(6)-fluoro-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-yl]amino}-1-piperidinecarboxylate and 300 parts of hydrobromic acid solution 48% in glacial acetic acid is stirred and refluxed for 1 hour. The reaction mixture is evaporated and the residue is boiled in 2-propanol. 2,2'-Oxybispropane is added and upon cooling, the product is allowed to crystallize. It is filtered off and dried, yielding 7.2 parts (88.2%) of 5(6)-fluoro-1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydro bromide; mp. 285.6° C.

EXAMPLE XVIII

Following the procedure of Example the following 1-R^2-N-(4-piperidinyl)-1H-benzimidazol-2-amines are prepared by hydrolysing the corresponding methyl or ethyl 1-piperidinecarboxylates.



R	R^1	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
H	H	H	5-Cl	CH	2HBr	—
H	H	H	H	CH	2HBr	—
H	H	CH_3	5(6)-CH_3	CH	2HBr	—
H	H	H	5-CH_3	CH	2HBr	—
H	H	CH_3	H	CH	2HBr	—
H	H	C_2H_5	H	CH	2HBr . $\frac{1}{2}H_2O$	334°-338° C.
H	H	nC_3H_7	H	CH	2HBr	—
H	H	$C_6H_5-CH_2$	H	CH	2HBr	—
H	H	nC_5H_{11}	H	CH	base	—
H	H	nC_7H_{15}	H	CH	base	—
H	H	nC_4H_9	H	CH	base	—
H	H	nC_6H_{13}	H	CH	base	—
H	H		H	CH	base	—
H	H	iC_3H_7	H	CH	base	—
H	CH_3	H	H	CH	2HBr . H_2O	—
H	H	2-Cl-$C_6H_4-CH_2$	H	CH	base	—
H	H	4-Cl-$C_6H_4-CH_2$	H	CH	2HBr . H_2O	—
H	H	4-Br-$C_6H_4-CH_2$	H	CH	2HBr . H_2O	>300° C.
H	H	4-CH_3-$C_6H_4-CH_2$	H	CH	2HBr	—
H	H	4-F-$C_6H_4-CH_2$	H	CH	2HBr	—
H	nC_4H_9	H	H	CH	2HBr . H_2O	223.1° C.
H	H	2-F-$C_6H_4-CH_2$	H	CH	2HBr	—
H	H	$C_6H_5-CH_2$	5-CF_3	CH	2HBr	—
H	H	$C_6H_5-CH_2$	5-Cl	CH	2HBr	>260° C.
H	H	$C_6H_5-CH_2$	H	N	2HCl . H_2O	298.1° C.
H	H	4-F-$C_6H_4-CH_2$	5-Cl	CH	2HBr	>260° C.
H	H	4-F-$C_6H_4-CH_2$	5(6)-CH_3	CH	2HBr	—
H	H	$C_6H_5-CH_2$	5(6)-CH_3	CH	2HBr	—
H	H	$C_6H_5-CH_2$	5(6)-F	CH	2HBr	>260° C.
3-CH_3	H	4-F-$C_6H_4-CH_2$	H	CH	2HBr	—
3-CH_3	H	$C_6H_5-CH_2$	H	CH	2HBr . H_2O	250.2° C. (cis + trans-isomer)
H	H	C_6H_5	H	CH	2HBr . H_2O	>300° C.
H	H	4-F-C_6H_4	H	CH	2HBr	>300° C.
H	H	4-NO_2-$C_6H_4-CH_2$	H	CH	2HBr	—
H	H	4-F-2-CH_3-$C_6H_3-CH_2$	H	CH	2HBr	—

EXAMPLE XIX

A mixture of 20 parts of (phenylmethyl) 4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridine-2-ylamino]-1-piperidinecarboxylate and 160 parts of methanol is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is boiled in 2,2'-oxybispropane. The undissolved product is filtered off and converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 12 parts of 3-(4-fluorophenylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrochloride monohydrate; mp. 269.7° C.

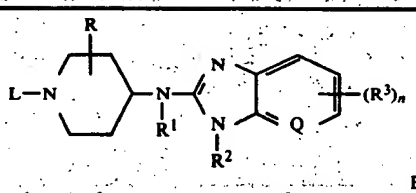
B. PREPARATION OF FINAL PRODUCTS:

EXAMPLE XX

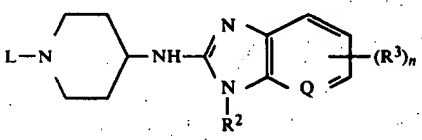
A mixture of 2 parts of 2-(bromoethoxy)benzene, 3 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine, 2 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70° C. The reaction mixture is cooled and poured onto water. The product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 3.5 parts (70%) of N-[1-(2-phenoxyethyl)-4-piperidinyl]-1-(phenylmethyl)-1H-benzimidazol-2-amine dihydrochloride monohydrate; mp. 197.6° C.

EXAMPLE XXI

Following the procedure of Example XX and using equivalent amounts of the appropriate starting materials the following compounds are prepared in free base form or in the form of an acid addition salt after reacting the free base with an appropriate acid.

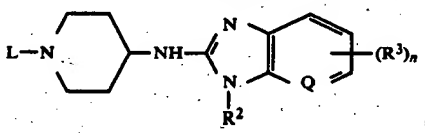


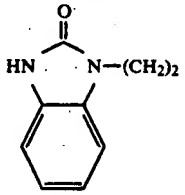
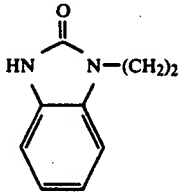
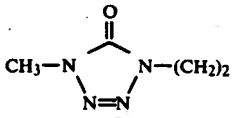
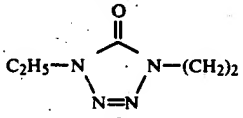
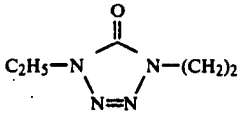
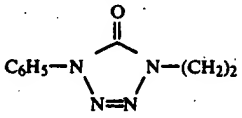
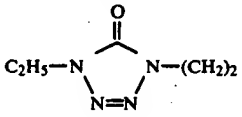
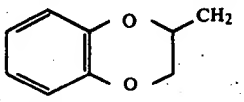
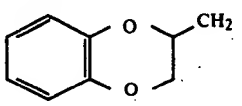
L	R	R^1	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
$C_6H_5-(CH_2)_2$	H	H	CH_3	H	CH	2HCl . ½ H_2O	298.3° C.
$C_6H_5-(CH_2)_2$	H	H	C_2H_5	H	CH	base	192.8° C.
$C_6H_5-(CH_2)_2$	H	H	nC_3H_7	H	CH	2HCl . ½ H_2O	278.8° C.
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	H	CH	base	141.9° C.
$C_6H_5-(CH_2)_2$	H	H	nC_5H_{11}	H	CH	2HCl . H_2O	243.5° C.
$C_6H_5-(CH_2)_2$	H	H	nC_7H_{15}	H	CH	2HCl . H_2O	212.8° C.
$C_6H_5-(CH_2)_2$	H	H	nC_4H_9	H	CH	2HCl . ½ H_2O	274.4° C.
$C_6H_5-(CH_2)_2$	H	H	nC_6H_{13}	H	CH	2HCl . H_2O	224.2° C.
$C_6H_5-(CH_2)_2$	H	H		H	CH	2HCl . ½ H_2O	285.6° C.
$C_6H_5-(CH_2)_2$	H	H	iC_3H_7	H	CH	2HCl	295.8° C.
$C_6H_5-(CH_2)_2$	H	CH_3	H	H	CH	2HCl	299.6° C.
$C_6H_5-(CH_2)_2$	H	H	2-Cl-$C_6H_4-CH_2$	H	CH	2HCl . ½ H_2O	244.4° C.
$C_6H_5-(CH_2)_2$	H	H	4-Br-$C_6H_4-CH_2$	H	CH	2HCl . H_2O	251.5° C.
$C_6H_5-(CH_2)_2$	H	H	4-$CH_3-C_6H_4-CH_2$	H	CH	2HCl . H_2O	191.4° C.
$C_6H_5-(CH_2)_2$	H	H	4-F-$C_6H_4-CH_2$	H	CH	2HCl	281.1° C.
$C_6H_5-(CH_2)_2$	H	nC_4H_9	H	H	CH	base	183.4° C.
$C_6H_5-(CH_2)_2$	H	H	2-F-$C_6H_4-CH_2$	H	CH	base	138.6° C.
$C_6H_5-(CH_2)_2$	H	H	H	H	CH	base	192.1° C.
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	5-CF_3	CH	2HCl	264.7° C.
$C_6H_5-(CH_2)_2$	H	H	4-F-$C_6H_4-CH_2$	5-Cl	CH	base	168.3° C.
$C_6H_5-(CH_2)_2$	H	H	4-F-$C_6H_4-CH_2$	5(6)-CH_3	CH	base	203°-215° C.
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	5(6)-CH_3	CH	base	181.9° C.
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	5(6)-F	CH	base . ½ H_2O	146.1° C.
$C_6H_5-(CH_2)_2$	H	H	4-F-$C_6H_4-CH_2$	H	N	base	193.2° C.
$C_6H_5-(CH_2)_2$	CH_3	H	$C_6H_5-CH_2$	H	CH	2HCl . H_2O	297.9° C. (cis + trans-isomer)
$C_6H_5-(CH_2)_2$	CH_3	H	4-F-$C_6H_4-CH_2$	H	CH	2HCl . H_2O	220.3° C. (cis + trans-isomer)
4-$NO_2-C_6H_4-(CH_2)_2$	H	H	4-F-$C_6H_4-CH_2$	H	CH	base	162.7° C.
$C_6H_5-(CH_2)_3$	H	H	$C_6H_5-CH_2$	H	CH	2HCl . H_2O	197.1° C.
$CH_2=CH-CH_2$	H	H	C_2H_5	H	CH	2HNO_3 . ½ H_2O	258.1° C.
$CH_2=CH-CH_2$	H	H	$C_6H_5-CH_2$	H	CH	2HCl . H_2O	261.9° C.
$C_6H_5-O-(CH_2)_3$	H	H	$C_6H_5-CH_2$	H	CH	2HCl . ½ H_2O	208.8° C.
$C_6H_5-O-(CH_2)_3$	H	H	4-F-$C_6H_4-CH_2$	H	CH	base	144.5° C.
$C_6H_5-O-(CH_2)_3$	H	H	4-F-$C_6H_4-CH_2$	H	N	base	157.6° C.
$C_6H_5-O-(CH_2)_3$	CH_3	H	4-F-$C_6H_4-CH_2$	H	CH	2$(COOH)_2H_2O$	141.3° C.
$(C_6H_5)_2CH-(CH_2)_2$	H	H	$C_6H_5-CH_2$	H	CH	base	173.8° C.
nC_4H_9	H	H	$C_6H_5-CH_2$	H	CH	2HCl . H_2O	273.3° C.
$C_6H_5-CO-CH_2$	H	H	$C_6H_5-CH_2$	H	CH	2HNO_3 . $3H_2O$	135.6° C.
$(C_6H_5)_2CH$	H	H	$C_6H_5-CH_2$	H	CH	base	203.7° C.
$C_6H_5-CH(CH_3)$	H	H	$C_6H_5-CH_2$	H	CH	base	154.0° C.
$C_6H_5-CH(CH_3)-CH_2$	H	H	$C_6H_5-CH_2$	H	CH	2HNO_3 . H_2O	159.0° C.
$C_6H_5-CH(CH_3)$	H	H	4-F-$C_6H_4-CH_2$	H	CH	base	170°-172.8° C.
$C_6H_5-CH(CH_3)-CH_2$	H	H	4-F-$C_6H_4-CH_2$	H	CH	$2HNO_3-2H_2O$	155.4° C.



L	R^2	$(R^3)_n$	Q	Base or salt form	melting point
4-$CH_3O-C_6H_4-O-(CH_2)_3$	4-F-$C_6H_4-CH_2$	H	CH	base	143.1° C.
$C_6H_5-CH=CH-CH_2$	4-F-$C_6H_4-CH_2$	H	CH	base . H_2O	155.5° C.
$C_6H_5-CH=CH-CH_2$	$C_6H_5-CH_2$	H	CH	2HCl . H_2O	192.4° C.
$C_6H_5-CH=CH-CH_2$	C_2H_5	H	CH	2HNO_3 . $2H_2O$	136.0° C.
$C_6H_5-CH=CH-CH_2$	4-F-$C_6H_4-CH_2$	H	N	base	152.8° C.
$C_6H_5-O-(CH_2)_4$	4-F-$C_6H_4-CH_2$	H	CH	base	150.7° C.
4-F-$C_6H_4-CO-(CH_2)_3$	$C_6H_5-CH_2$	H	CH	2HCl . ½H_2O	269.1° C.

-continued



L	R^2	$(R^3)_n$	Q	Base or salt form	melting point
4-F—C_6H_4—CO—$(CH_2)_3$	C_2H_5	H	CH	2HCl	293.1° C.
C_6H_5—CH_2	CH_3	H	CH	2HCl . $2H_2O$	241.0° C.
C_6H_5—CH_2	C_6H_5—CH_2	H	CH	$2HNO_3$. $2H_2O$	147.2° C.
4-F—C_6H_4—CH_2	C_6H_5—CH_2	H	CH	base	152.1° C.
$C_6H_5(CH_2)_2$	4-Cl—C_6H_4—CH_2	H	CH	2HCl . $\frac{1}{2}H_2O$	277.1° C.
4-F—C_6H_4—$(CH_2)_2$	4-F—C_6H_4—CH_2	H	CH	2HCl . $\frac{1}{2}H_2O$	283.7° C.
4-F—C_6H_4—$(CH_2)_2$	C_6H_5—CH_2	H	CH	base	112.5° C.
3-CF_3—C_6H_4—$(CH_2)_2$	C_6H_5—CH_2	H	CH	base	140.3° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$—	H	H	CH	2HCl . $\frac{1}{2}H_2O$	279.4° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$—	H	5-Cl	CH	2HCl	194.8° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$—	H	5-CH_3	CH	2HCl . $\frac{1}{4}CH_3CHOHCH_3$	171.8° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$—	C_6H_5—CH_2	H	CH	$2HNO_3.H_2O$	230.9° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$—	CH_3	H	CH	2HCl . H_2O	271.7° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$—	CH_3	5(6)-CH_3	CH	2HCl . H_2O	245.8° C.
$(4\text{-F—}C_6H_4)_2CH$—$(CH_2)_3$	C_2H_5	H	CH	2HCl . $2H_2O$	208.6° C.
	C_6H_5—CH_2	H	CH	base	237.5° C.
	C_2H_5	H	CH	base	227.0° C.
	4-F—C_6H_4—CH_2	H	CH	2HCl . H_2O	192.9° C.
	C_6H_5—CH_2	H	CH	2HCl . H_2O	170.9° C.
	4-F—C_6H_4—CH_2	H	CH	base	146.5° C.
	CH_3	H	CH	2HCl . $\frac{1}{2}H_2O$	279.6° C.
	4-F—C_6H_4—CH_2	H	N	base	143.4° C.
(4-F—C_6H_4)$_2$—CH—$(CH_2)_3$	(4-F—C_6H_4)$_2$—CH—$(CH_2)_3$	H	CH	base	171.1° C.
	C_2H_5	H	CH	$2HNO_3$. H_2O	266.5° C.
	C_6H_5—CH_2	H	CH	base	210.2° C.

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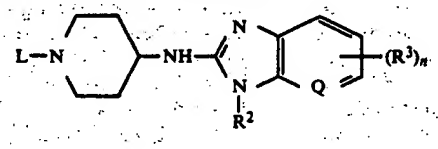
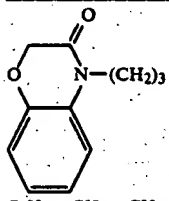
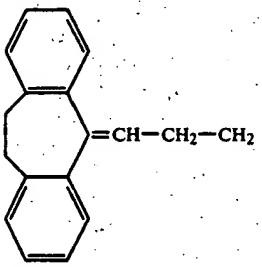
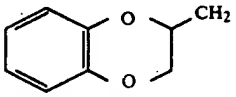
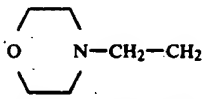


L	R^2	$(R^3)_n$	Q	Base or salt form	melting point
	$C_6H_5-CH_2$	H	CH	2. $HOOC-CH=CH-COOH$	196.2° C.
$C_6H_5-CH_2-CH_2$	$C_6H_5-CH_2$	5-Cl	CH	base	126.4° C.
$C_6H_5-NH-(CH_2)_3$	4-F-$C_6H_4-CH_2$	H	CH	base	153.1° C.
$C_6H_5-O-(CH_2)_3$	C_6H_5	H	CH	base	130.0° C.
$C_6H_5-CH_2-CH_2$	C_6H_5	H	CH	base	131.0° C.
$CH_3-(CH_2)_3$	C_6H_5	H	CH	base	125.3° C.
$C_6H_5-CH=CH-CH_2$	C_6H_5	H	CH	base	147.1° C.
$C_6H_5-CH_2-CH_2$	4-F-C_6H_4	H	CH	base	113.8° C.
$C_6H_5-O-(CH_2)_3$	4-F-C_6H_4	H	CH	base	105.6° C.
4-$CH_3O-C_6H_4-S-(CH_2)_3$	4-F-$C_6H_4-CH_2$	H	CH	base	114.5° C.
$C_6H_5-CH_2-CH_2$	$C_6H_5-CH_2$	H	N	base	153.2° C.
	4-F-$C_6H_4-CH_2$	H	CH	base	177.6° C.
4-(CH_3-S)-$C_6H_4-(CH_2)_2$	4-F-$C_6H_4-CH_2$	H	CH	base	176.0° C.
4-(CH_3-SO_2)-$C_6H_4-(CH_2)_2$	4-F-$C_6H_4-CH_2$	H	CH	½ $CH_3-CH(OH)-CH_3$	235.8° C.
(4-F-$C_6H_4)_2-CH-(CH_2)_3$	4-F-$C_6H_4-CH_2$	H	CH	base	131.9° C.
$CH_3-(CH_2)_3$	$C_6H_5-CH_2$	H	N	base	147.5° C.
$C_6H_5-O-CH_2-CH_2$	$C_6H_5-CH_2$	H	N	base	142.5° C.
$(C_6H_5)_2-CH-CH_2-CH_2$	$C_5H_5-CH_2$	H	N	base	141.4° C.
$NC-CH_2$	4-F-$C_6H_4-CH_2$	H	CH	base	178.7° C.
4-F-$C_6H_4-CO-(CH_2)_3$	4-F-$C_6H_4-CH_2$	H	N	base	161.5° C.
4-F-$C_6H_4-O-(CH_2)_3$	$C_6H_5-CH_2$	H	N	base	124.9° C.
	$C_6H_5-CH_2$	H	N	base	184.7° C.
$CH_2=CH-CH_2$	$C_6H_5-CH_2$	H	N	base	132.6° C.
2,6-$(CH_3)_2-C_6H_3-CO-CH_2$	$C_6H_5-CH_2$	H	N	base	176.8° C.
	$C_6H_5-CH_2$	H	N	½ H_2O	153.3° C.
$C_6H_5-CH=CH-CH_2$	$C_6H_5-CH_2$	H	N	base	124.6° C.
4-F-$C_6H_4-CO-(CH_2)_3$	$C_6H_5-CH_2$	H	N	base	141.0° C.
$CH_3-(CH_3)_5$	$C_6H_5-CH_2$	H	N	base	137.3° C.
3-CN-3,3-$(C_6H_4)_2-C-(CH_2)_2$	4-F-$C_6H_4-CH_2$	H	N	2 HCl.H_2O	188.9° C.
3-CN-3,3-$(C_6H_4)_2-C-(CH_2)_2$	$C_6H_5-CH_2$	H	CH	2 HNO_3 . H_2O	151.1° C.
3-CN-3,3-$(C_6H_4)_2-C-(CH_2)_2$	CH_3-CH_2	H	CH	2 HNO_3 . ½H_2O	240.5° C.

EXAMPLE XXII

A mixture of 2.4 parts of (2-bromoethyl)benzene, 6 parts of 5(6)-fluoro-1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 4 parts of sodium carbonate, 0.2 parts of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight using a water-separator. The reaction mixture is cooled and poured onto water. The layers are separated and the aqueous phase is extracted three times with trichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is separated by column-chromatography over silica gel

using a mixture of ethyl acetate and methanol (93:7 by volume) as eluent. The first fraction (A-isomer) is collected and the eluent is evaporated. The residue is washed with a mixture of 2,2'-oxybispropane and petroleumether, and dried, yielding 1 part (17.5%) of 6-fluoro-1-(4-fluorophenylmethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 178.1° C.

The second fraction (B-isomer) is collected and the eluent is evaporated. The residue is washed with a mixture of 2,2'-oxybispropane and petroleumether, and dried, yielding 1.2 parts of 5-fluoro-1-(4-fluorophenylmethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine monohydrate; mp. 188.8° C.

EXAMPLE XXIII

A mixture of 4 parts of 1-(3-chloropropyl)-1,3-dihydro-3-(1-methylethenyl)-2H-benzimidazol-Z-one, 7 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 5 parts of sodium carbonate, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70° C. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanol. After stirring for 1 hour, the solvent is evaporated and the residue is taken up in water. The free base is liberated in the conventional manner with ammonium hydroxide and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from ethanol. The product is filtered off and dried, yielding 3.3 parts (45.7%) of 1,3-dihydro-1-[3-{4-[1-(phenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl{propyl]-2H-benzimidazol-2-one; mp. 243.1° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

1-[3-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 237.6° C.;

1-[3-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-3-methyl-1-piperidinyl}-propyl]-1,3-dihydro-2H-benzimidazol-2-one dihydrochloride. 2-propanolate (1:1); mp. 244.1° C.;

1-[3-{4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinyl}propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 202.4° C.;

1,3-dihydro-1-{3-[4-(1-phenyl-1H-benzimidazol-2-ylamino)-1-piperidinyl]propyl}-2H-benzimidazol-2-one; mp. 185.3° C.;

1-[3-{4-[1-(4-fluorophenyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}propyl]-1,3-dihydro-2H-benzimidazol-2-one; 188.9° C.; and

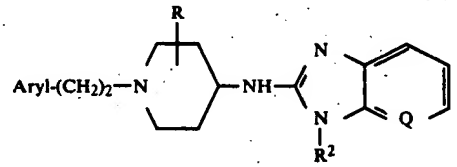
1,3-dihydro-1-[3-{4-[3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinyl}-propyl]-2H-benzimidazol-2-one; mp. 221.7° C.

EXAMPLE XXIV

A mixture of 2.3 parts of 2-(4-methoxyphenyl)ethyl methanesulfonate, 4.9 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 3.2 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70° C. The reaction mixture is poured onto water. The product is extracted with methylbenzene. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2'-oxybispropane, yielding 2.2 parts (48%) of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine; mp. 172.9° C.

EXAMPLE XXV

Following the procedure of Example XXIV and using equivalent amounts of the appropriate starting materials the following compounds are obtained in free base form or in the form of an acid addition salt after reacting the free base with an appropriate acid.



Aryl	R	R^2	Q	Base or salt form	melting point
3,4-$(CH_3O)_2$—C_6H_3	H	4-F—C_6H_4—CH_2	CH	base	69.3° C.
2,5-$(CH_3O_2$—C_6H_3	H	4-F—C_6H_4—CH_2	CH	base	127.9° C.
4-(C_2H_5O)—C_6H_4	H	4-F—C_6H_4—CH_2	CH	base	152.3° C.
4-(CH_3O)—C_6H_4	H	4-F—C_6H_4—CH_2	N	base	149.1° C.
3-(CH_3O)—C_6H_4	H	4-F—C_6H_4—CH_2	CH	2HCl . ½ H_2O	242.4° C.
2-(CH_3O)—C_6H_4	H	4-F—C_6H_4—CH_2	CH	base	158.1° C.
4-(CH_3O)—C_6H_4	CH_3	4-F—C_6H_4—CH_2	CH	2HCl	184.0° C. (cis+trans-isomer)
3,4,5-$(CH_3O)_3$—C_6H_2	H	4-F—C_6H_4—CH_2	CH	2HCl . ½ H_2O	260.2° C.
3,4-$(CH_3O)_2$—C_6H_3	H	C_6H_5—CH_2	CH	base	149.8° C.
4-(CH_3O)—C_6H_4	CH_3	C_6H_5—CH_2	CH	2HClH_2O	198.4° C. (cis+trans-isomer)
3-(CH_3O)—C_6H_4	H	C_6H_5—CH_2	CH	base	128.6° C.
4-(C_2H_5O)—C_6H_4	H	C_6H_5—CH_2	CH	base	128.5° C.

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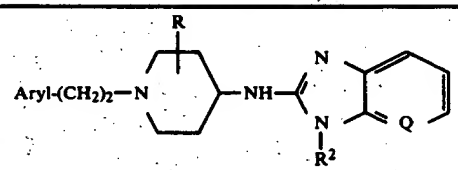
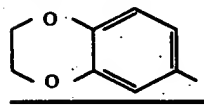


Aryl	R	R^2	Q	Base or salt form	melting point
2-(CH_3O)—C_6H_4	H	C_6H_5—CH_2	CH	2HCl . $2H_2O$	186.1° C.
3-(CH_3)—C_6H_4	H	C_6H_5—CH_2	CH	2HCl . H_2O	235.7° C.
4-(CH_3O)—C_6H_4	H	C_6H_5—CH_2	CH	2HCl . H_2O	274.7° C.
4-Cl—C_6H_4	H	C_6H_5—CH_2	CH	base	183.9° C.
3,4,5-(CH_3O)$_3$—C_6H_2	H	C_6H_5—CH_2	CH	base	156.6° C.
4-($C_6H_5CH_2O$)—C_6H_4	H	4-F—C_6H_4—CH_2	CH	base	155.4° C.
4-CH_3O—C_6H_4	H	C_6H_5	CH	base	157.8° C.
4-CH_3O—C_6H_4	H	4-F—C_6H_4	CH	base	167.4° C.
4-CH_3O—C_6H_4	H	4-NO_2—C_6H_4—CH_2	CH	base	200.1° C.
2,4-(CH_3O)$_2$—C_6H_3	H	4-F—C_6H_4—CH_2	CH	2HCl . $\frac{1}{2}H_2O$	190.4° C.
4-CH_3O—C_6H_4	H	4-F-2-CH_3—C_6H_3—CH_2	CH	2HBr	264.8° C.
4-CH_3O—C_6H_4	H	C_6H_5—CH_2	N	base	124.1° C.
3-CH_3-4-(C_6H_5—CH_2—O)—C_6H_3	H	4-F—C_6H_4—CH_2	CH	base	145.6° C.
	H	4-F—C_6H_4—CH_2	CH	2HCl . H_2O	264.6° C.

EXAMPLE XXVI

A mixture of 2.8 parts of [2-(2-thienyl)ethyl]4-methylbenzenesulfonate, 4.9 parts of 1-[4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 2.1 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70° C. The reaction mixture is cooled and poured onto water. The product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanol. The product is filtered off and dried, yielding 2.3 parts (53%) of 1-(4-fluorophenylmethyl)-N-{1-[2-(2-thienyl-)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine; mp. 151.6° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

1-(phenylmethyl)-N-{1-[2-(2-thienyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine dihydrochloride. monohydrate; mp. 259°-273° C.;

1-(4-fluorophenylmethyl)-N-{1-[2-(1-naphthalenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine; mp. 143.1° C.; and

3-(4-fluorophenylmethyl)-N-{1-[2-(2-thienyl)ethyl]-4-piperidinyl}-3H-imidazo[4,5-b]pyridin-2-amine; mp. 176.2° C.

EXAMPLE XXVII

A mixture of 2.1 parts of 2-(ethenyl)pyridine, 3.25 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine and 80 parts of 1-butanol is stirred and refluxed overnight. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2'-oxybispropane, yielding 1 part (23%) of 1-[(4-fluorophenyl)-methyl]-N-{1-[2-(2-pyridinyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine; mp. 133.4° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinepropanenitrile; mp. 166.5° C.;

1-(4-fluorophenylmethyl)-N-{1-[2-(4-pyridinyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine; mp. 158.2° C.; and

3-(4-fluorophenylmethyl)-N-{1-[2-(2-pyridinyl)ethyl]-4-piperidinyl}-3H-imidazo[4,5-b]pyridin-2-amine; mp. 157.2° C.

EXAMPLE XXVIII

To 3.96 parts of 1-(4-fluorobenzoyl)aziridine, dissolved in 16 parts of benzene, are added 3.25 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine, 90 parts of benzene and 45 parts of N,N-dimethylformamide. The whole is stirred and refluxed for 5 hours. The reaction mixture is cooled and poured onto water. The layers are separated and the aqueous phase is extracted with methylbenzene. The combined organic phases are dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1part (19%) of 4-fluoro-N-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]benzamide; mp. 193.7° C.

Starting from 3-(phenylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine and following the same procedure there is also prepared:

4-fluoro-N-[2-{4-[3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinyl}ethyl]benzamide; mp. 187.5° C.

EXAMPLE XXIX

A mixture of 3.6 parts of [(4-methoxyphenoxy)methyl]oxirane, 4.9 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 2.1 parts of sodium carbonate, 40 parts of methanol and 90 parts of benzene is stirred and refluxed overnight. The reaction mixture is filtered and the filtrate is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 2.6 parts (51%) of 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-α-(4-methoxyphenoxymethyl)-1-piperidineethanol; mp. 174.5° C.

EXAMPLE XXX

Following the procedure of Example XXIX and using equivalent amounts of the appropriate starting materials there are also prepared:

α-(phenoxymethyl)-4-{[1-(phenylmethyl)-1H-benzimidazol-2-yl]amino}-1-piperidineethanol; mp. 146.6° C.;

4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-α-(phenoxymethyl)-1-piperidineethanol; mp. 181.3° C.;

4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-3-methyl-α-(phenoxymethyl)-1-piperidineethanol dihydrochloride. monohydrate; mp. 163.3° C.;

α-(4-methoxyphenoxymethyl)-4-[1-(phenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol; mp. 162.7° C.;

α-(2-butoxyphenoxymethyl)-4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol; mp. 138.7° C.;

α-(2,6-dimethoxyphenoxymethyl)-4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol; mp. 140° C.;

4-[1-(3-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-α-(2-methoxyphenoxymethyl)-1-piperidineethanol; mp. 174° C.;

1-{4-[3-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}-2-hydroxypropoxy]-phenyl}ethanone; mp. 174.7° C.;

α-(2,6-dimethoxyphenoxymethyl)-4-[1-(phenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol; mp. 122.2° C.;

4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-α-phenyl-1-piperidineethanol; mp. 184.1° C.; and

α-(phenoxymethyl)-4-[3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidineethanol; mp. 136.6° C.

EXAMPLE XXXI

To a stirred mixture of 40.4 parts of 1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine hydrobromide and 400 parts of methanol are added 8.8 parts of oxirane and stirring is continued overnight at room temperature. The reaction mixture is evaporated and the residue is taken up in water. The precipitated product is filtered off and dried, yielding 29 parts (64%) of 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol monohydrobromide; mp. 248.2° C.

EXAMPLE XXXII

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol, are added 1.5 parts of formaldehyde solution 37%, 3 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The residue is taken up in water and the whole is alkalized with ammonium hydroxide. The product is extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 1.5 parts (36.6%) of N-(1-methyl-4-piperidinyl)-1-(phenylmethyl)-1H-benzimidazol-2-amine dihydrochloride monohydrate; mp. 191.1° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

1-(4-fluorophenylmethyl)-N-(1-methyl-4-piperidinyl)-1H-benzimidazol-2-amine; mp. 145.5° C.;

N-(1-cyclohexyl-4-piperidinyl)-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine; mp. 168° C.;

1-(4-fluorophenylmethyl)-N-[1-(1-methyl-2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 182.4° C.;

1-methyl-N-(1-methyl-4-piperidinyl)-1H-benzimidazol-2-amine dihydrochloride dihydrate; 300.6° C.;

1-ethyl-N-[1-methylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 156.6° C.

N-(1-methyl-4-piperidinyl)-1-phenyl-1H-benzimidazol-2-amine; mp. 128.5° C.

3-(4-fluorophenylmethyl)-N-(1-methyl-4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 153.4° C.; and

N-(1-methyl-4-piperidinyl)-3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 141.4° C.

EXAMPLE XXXIII

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol, are added 2 parts of cyclohexanone, 3 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine, 1 part of acetic acid and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The residue is taken up in water and the whole is alkalized with sodium hydroxide. The product is extracted with tetrahydrofuran. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2,2'-oxybispropane and 2-propanol, yielding 1.5 parts (38.5%) of N-(1-cyclohexyl-4-piperidinyl)-1-(phenylmethyl)-1H-benzimidazol-2-amine; amine; mp. 143° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

1-phenyl-4-{4-[1-(phenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}cyclohexanecarbonitrile; mp. 106°-107° C.;

4-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}-1-phenylcyclohexanecarbonitrile dihydrochloride; mp. 275° C.;

1-[3-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}butyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 234.8° C.;
N-(1-cyclohexyl-4-piperidinyl)-3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 129.2° C.;
N-[1-(1-methylethyl)-4-piperidinyl]-3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 136.4° C.; and
1-(4-fluorophenylmethyl)-N-[1-{2-[(phenylmethyl-)amino]ethyl}-4-piperidine]-1H-benzimidazol-2-amine; mp. 135.6° C.

EXAMPLE XXXIV

A mixture of 39.8 parts of N-(2-aminophenyl)-N'-ethyl-N'-[I-(2-phenylethyl)-4-piperidinyl]thiourea, 15 parts of mercury oxide, 0.1 parts of sulfur and 400 parts of methanol is stirred and refluxed overnight. The reaction mixture is filtered hot over Hyflo and the filtrate is evaporated. The residue is crystallized from 4-methyl-2-pentanone. The product is filtered off and dried, yielding 14.5 parts (43%) of N-ethyl-N-[I-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 204.9° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:
N-[1-(2-phenylethyl)-4-piperidinyl]-N-propyl-1H-benzimidazol-2-amine;
N-(1-methylethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 228.4° C.;
N-cyclopropyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 193.5° C.;
N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 191.5° C.

EXAMPLE XXXV

To a stirred and cooled (below 5° C.) mixture of 3.3 parts of N-methyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine, 100 parts of dimethylsulfoxide and 90 parts of benzene are added 0.5 parts of sodium hydride dispersion 50%. After stirring for 30 minutes, 1.5 parts of 1-(chloromethyl)-4-fluorobenzene are added and stirring is continued overnight while the mixture is allowed to reach room temperature. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from 2-propanol, yielding 2.8 parts (54.4%) of 1-[(4-fluorophenyl)methyl]-N-methyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine dihydrochloride; mp. 246.6° C.

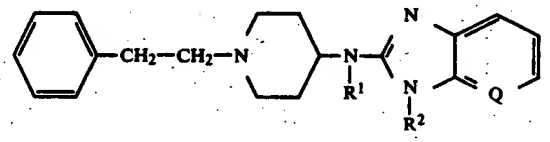
Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:
1-[(4-chlorophenyl)methyl]-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 138° C.;
1-[(2-methoxyphenyl)methyl]-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 148.3° C.;
1-[(4-methoxyphenyl)methyl]-N[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 122.4° C.;
1-[(4-fluorophenyl)methyl]-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 108.5° C.;
1-(4-bromophenylmethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 139.3° C.;
1-[(4-methylphenyl)methyl]-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 123.4° C.;
1-(2-chlorophenylmethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 105.5° C.;
1-butyl-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 76.5° C.; and
1-ethyl-N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine dihydrochloride. dihydrate; mp. 157.2° C.

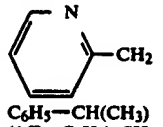
EXAMPLE XXXVI

A mixture of 1.6 parts of 1-(1-chloroethyl)-4-fluorobenzene, 3.2 parts of N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine, 1 part of sodium carbonate, 0.1 parts of potassium iodide and 120 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2'-oxybispropane. The product is filtered off and dried, yielding 1.8 parts (40.7%) of 1-[1-(4-fluorophenyl)ethyl]-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 161.7° C.

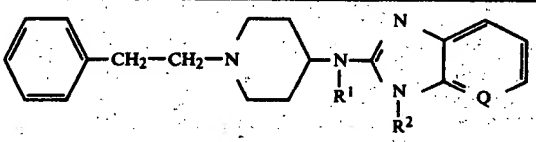
EXAMPLE XXXVII

Following the procedures of Examples XXXV and XXXVI and using equivalent amounts of the appropriate starting materials the following compounds are obtained in free base form or in the form of an acid addition salt after reacting the free base with an appropriate acid



R^1	R^2	Base or Salt form	melting point
H	$C_6H_5-(CH_2)_2$	base	136.1° C.
H	$4\text{-}F-C_6H_4-(CH_2)_2$	base	151.5° C.
H	$(4\text{-}F-C_6H_5)-CH(C_6H_5)$	2HCl . H_2O	239.6° C.
H	$C_6H_5-CH(CH_3)-CH_2$	base	144.5° C.
H		base	127.6° C.
H	$C_6H_5-CH(CH_3)$	2HCl . H_2O	239.9° C.
H	$(4\text{-}F-C_6H_4)_2CH$	base	172.5° C.
H	$2\text{-}(CH_3O)-C_6H_4-CH_2$	base	128.5° C.
CH_3	$2\text{-}(CH_3O)-C_6H_4-CH_2$	$2HNO_3$	169.7° C.
CH_3	$2\text{-}Cl-C_6H_4-CH_2$	2HCl	251.2° C.
CH_3	$4\text{-}Br-C_6H_4-CH_2$	2HCl . H_2O	187.1° C.
CH_3	$4\text{-}(CH_3O)-C_6H_4-CH_2$	$2HNO_3$	163.5° C.
CH_3	$C_6H_5-CH_2$	2HCl	243.1° C.
CH_3	$4\text{-}(CH_3)-C_6H_4-CH_2$	$2HNO_3$	175.3° C.
CH_3	$4\text{-}Cl-C_6H_4-CH_2$	2HCl	251.3° C.
CH_3	n. C_4H_9	2HCl	257.9° C.
CH_3	C_2H_5	2HCl . H_2O	243.1° C.
C_2H_5	$C_6H_5-CH_2$	base	115.8° C.
C_2H_5	C_2H_5	base	93.2° C.
nC_3H_7	$C_6H_5-CH_2$	2HCl . H_2O	159.4° C.
nC_3H_7	nC_4H_9	$(COOH)_2$	177.5° C.
nC_3H_7	C_2H_5	2HCl	160.7° C.

-continued



R^1	R^2	Base or Salt form	melting point
iC_3H_7	C_2H_5	2HCl . ½ H_2O	206.8° C.
iC_3H_7	$C_6H_5—CH_2$	$(COOH)_2$	215.6° C.
iC_3H_7	nC_4H_9	$(COOH)_2$	198.0° C.
nC_4H_9	$C_6H_5—CH_2$	2HCl . $2H_2O$	160.0° C.
nC_4H_9	$4\text{-}Br—C_6H_4—CH_2$	2HCl . $2H_2O$	137.2° C.
nC_4H_9	nC_4H_9	2HCl . $2H_2O$	138.7° C.
nC_4H_9	$4\text{-}F—C_6H_4—CH_2$	2HCl . $2H_2O$	135.5° C.
	C_2H_5	2HCl . $2H_2O$	123.8° C.

EXAMPLE XXXVIII

A mixture of 3.2 parts of N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine, 2.9 parts of [2-(2-thienyl)ethyl] 4-methylbenzenesulfonate, 1 part of sodium carbonate and 135 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2,2'-oxybispropane and 2-propanone, yielding 1 part (23.2%) of N-[1-(2-phenylethyl)-4-piperidinyl]-1-[2-(2-thienyl)ethyl]-1H-benzimidazol-2-amine; mp. 118.3° C.

EXAMPLE XXXIX

To a stirred and cooled (below 5° C.) mixture of 4 parts of N-[1-(2-phenylethyl)-4-piperidinyl]-1-(phenylmethyl)-1H-benzimidazol-2-amine, 100 parts of dimethyl sulfoxide and 90 parts of benzene are added 0.5 parts of sodium hydride dispersion 50%. After stirring for 30 minutes at a temperature below 5° C., 1.3 parts of (chloromethyl)benzene are added and stirring is continued for 4 hours while the mixture is allowed to reach room temperature. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the nitrate salt in 2-propanone. The salt is filtered off and dried, yielding 1.5 parts (24%) of N-[1-(2-phenylethyl)-4-piperidinyl]-N,1-bis(phenylmethyl)-1H-benzimidazol-2-amine dinitrate; mp. 156.9° C.

EXAMPLE XL

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol are added 3.3 parts of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-nitrophenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of methylbenzene and methanol (95:5 by volume) saturated with ammonia, as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanol, yielding 1.3 parts (42%) of N-{1-[2-(4-aminophenyl)ethyl]-4-piperidinyl}-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine; mp. 195.4° C.

Following the same hydrogenation procedure and starting from the corresponding nitro-compound there is also prepared:

1-[(4-aminophenyl)methyl]-N-{1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine monohydrate; mp. 142.6° C.

EXAMPLE XLI

A mixture of 7.5 parts of 1-(4-fluorophenylmethyl)-N-[1-{2-[4-(phenylmethoxy)phenyl]ethyl}-4-piperidinyl]-1H-benzimidazol-2-amine and 120 parts of methanol is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is suspended in 2,2'-oxybispropane. The product is filtered off and dried, yielding 5.5 parts (88.5%) of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol hemihydrate; mp. 111.6° C.

Following the same hydrogenation procedure and starting from 1-(4-fluorophenylmethyl)-N-[1-{2-[3-methyl-4-(phenylmethoxy)phenyl]ethyl}-4-piperidinyl]-1H-benzimidazol-2-amine there is also prepared 4-{2-[4-{[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-yl]amino}-1-piperidinyl]ethyl}-2-methylphenol dihydrochloride monohydrate; mp. 277.8° C.

A mixture of 8 parts of 1-(4-fluorophenylmethyl)-N-{1-[2-(3-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine and 225 parts of a hydrobromic acid solution 48% in acetic acid is stirred and refluxed for 3 hours. The reaction mixture is evaporated and the residue is taken up in water. The free base is liberated in the conventional manner with ammonium hydroxide and extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is purified twice by column-chromatography over silica gel using first a mixture of trichloromethane and methanol (98:2 by volume) and then a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 0.8 parts (9%) of 3-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-yl-amino]-1-piperidinyl}ethyl]phenol dihydrochloride. monohydrate; mp. 209.8° C.

EXAMPLE XLII

A mixture of 1.2 parts of 3-bromo-1-propene, 4 parts of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol, 1.4 parts of potassium carbonate and 160 parts of 2-propanone is stirred and refluxed overnight. The reaction mixture is filtered and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is

filtered off and dried, yielding 1 part (19.9%) of 1-(4-fluorophenylmethyl)-N-[1-{2-[4-(2-propenyloxy)-phenyl]ethyl}-4-piperidinyl]-1H-benzimidazo 1-2-amine dihydrochloride; mp. 224.7° C.

EXAMPLE XLIII

A mixture of 15 parts of thionyl chloride, 4 parts of 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol dihydrochloride and 375 parts of trichloromethane is stirred and refluxed overnight. The precipitated product is filtered off and dried, yielding 13 parts (83%) of N-[1-(2-chloroethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine dihydrochloride; mp. >260° C.

EXAMPLE XLIV

A mixture of 0.9 parts of morpholine, 4.8 parts of N-[1-(2-chloroethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine dihydrochloride, 3 parts of sodium carbonate, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70° C. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 0.6 parts (12.5%) of [2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl] 4-morpholinecarboxylate; mp. 144.8° C.

EXAMPLE XLV

A mixture of 3.6 parts of morpholine, 4.8 parts of N-[1-(2-chloroethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine dihydrochloride, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70° C. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in methanol. The salt is filtered off and dried, yielding 1 part (18.3%) of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-morpholinyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine trihydrochloride; mp. +300° C.

EXAMPLE XLVI

To a stirred mixture of 4.5 parts of 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol, 2 parts of N,N-diethylethanamine and 195 parts of dichloromethane is added dropwise a solution of 1.7 parts of 4-methoxybenzoyl chloride in dichloromethane. Upon completion, stirring is continued overnight at room temperature. Water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 2.5 parts (43.5%) of [2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl] 4-methoxybenzoate; dihydrochloride. hemihydrate; mp. 189.2° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}benzeneacetate; mp. 135.1° C.;

{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}4-methoxybenzoate; mp. 157.1° C.;

{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}methyl carbonate; mp. 134.5° C.; and

{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}(phenylmethyl) carbonate; mp. 147.8° C.

EXAMPLE XLVII

A mixture of 1.2 parts of chloroacetonitrile, 6.7 parts of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol, 2.8 parts of potassium carbonate and 160 parts of 2-propanone is stirred and refluxed overnight. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 7.4 parts (78.6%) of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy}acetonitrile dihydrochloride. monohydrate; mp. 224.6° C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

ethyl 2-{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy-}acetate; mp. 109.1° C.;

methyl 2-{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy-}acetate; mp. 109.8° C.; and

1-[2-{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy}acetyl]piperidine dihydrochloride; mp. 247° C.

EXAMPLE XLVIII

A mixture of 0.5 parts of isocyanatomethane, 4.5 parts of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol and 135 parts of tetrahydrofuran is stirred overnight at room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1 part (20%) of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-phenyl}methylcarbamate; mp. 172.2° C.

By the addition-reaction of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol to 1-isocyanatobutane there is also repared: {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}-butyl carbamate; mp. 142.5° C.

EXAMPLE IL

A mixture of 9 parts of 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineacetonitrile and 200 parts of methanol, saturated with ammonia, is

hydrogenated at normal pressure and at room temperature with 3 parts of Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from a mixture of 2-propanone and methanol, yielding 11 part of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine trihydrochloride; mp. 292.9° C.

Following the same hydrogenation procedure and starting from 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinepropanenitrile there is also prepared: N-[1-(3-aminopropyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine trihydrochloride. monohydrate; mp. 239.3° C.

EXAMPLE L

A mixture of 1.8 parts of 1-isothiocyanato-2-nitrobenzene, 3.7 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine and 135 parts of tetrahydrofuran is stirred overnight at room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 3.7 parts (67%) of N-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-N'-(2-nitrophenyl)thiourea as a residue.

A mixture of 3.7 parts of N-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-N'-(2-nitrophenyl)thiourea, 7 parts of iron-powder, 0.25 parts of concentrated hydrochloric acid, 48 parts of ethanol and 15 parts of water is stirred and refluxed for 1 hour. The reaction mixture is alkalized with methanol saturated with ammonia. The whole is filtered and the filtrate is evaporated, yielding 3.5 parts of N-(2-aminophenyl)-N'-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}-ethyl]thiourea as a residue.

A mixture of 3.5 parts of N-(2-aminophenyl)-N'-[2-}4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]thiourea, 2.2 parts of mercury (II) oxide, 0.1 parts of sulfur and 80 parts of ethanol is stirred and refluxed for 1 hour. The reaction mixture is filtered over Hyflo and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanone, yielding 1.5 parts (44.4%) of N-{1-[2-(1H-benzimidazol-2-ylamino)ethyl]-4-piperidinyl}-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine; mp. 253.4° C.

EXAMPLE LI

A solution of 4.77 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine trihydrochloride in methanol saturated with ammonia is stirred for 1 hour at room temperature. The solvent is evaporated and the residue is taken up in 135 parts of tetrahydrofuran. Then there are added 6 parts of isocyanatomethane and the whole is stirred overnight at room temperature. The precipitated product is filtered off and dried, yielding 3 parts (70.7%) of N-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-N'-methylurea. hemihydrate; mp. 231.4° C.

EXAMPLE LII

To a stirred mixture of 3.8 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine, 1 part of N,N-diethylethanamine and 195 parts of dichloromethane is added dropwise a solution of 1.7 parts of 4-methoxybenzoyl chloride in dichloromethane. Upon completion, stirring is continued overnight at room temperature. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 1 part of N-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-4-methoxy-N-(4-methoxybenzoyl)benzamide dihydrochloride. dihydrate; mp. 161.5° C.

EXAMPLE LIII

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol are added 1 part of paraformaldehyde, 3.5 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is taken up in water and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1.5 parts (42%) of N-{1-[2-(dimethylamino)ethyl]-4-piperidinyl}-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine; mp. 166.1° C.

EXAMPLE LIV

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol are added 2.5 parts of benzaldehyde, 3.7 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over hyflo and the filtrate is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and taken up in water. The free base is liberated in the conventional manner with ammonium hydroxide and extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1.5 parts (27.5%) of N-[1-{2-[bis(phenylmethyl)amino]ethyl}-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine; mp. 116.4° C.

EXAMPLE LV

A mixture of 5.5 parts of N-[1-(1H-benzimidazol-2-yl)-4-piperidinyl]-1-(phenylmethyl)-1H-benzimidazol-2-amine dinitrate, 1.5 parts of 1-(chloromethyl)-4-fluorobenzene, 5 parts of sodium carbonate, 0.1 parts of potas-

sium iodide and 120 parts of 4-methyl-2-pentanone is stirred and refluxed overnight using a water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 1.5 parts (28.3%) of N-{1-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-yl]-4-piperidinyl}-1-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 163.9° C.

EXAMPLE LVI

A mixture of 3.7 parts of 1-(4-fluorophenylmethyl)-N-{1-[3-(4-methoxyphenylthio)propyl]-4-piperidinyl}-1H-benzimidazol-2-amine, 2.42 parts of hydrogen peroxide solution 30% and 20 parts of acetic acid is stirred and refluxed for 1 hour. The reaction mixture is cooled and poured onto ice-water. The whole is alkalized with sodium hydroxide solution 50% and the product is extracted with trichloromethane. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the ethanedioate salt in methanol and 2-propanol. The salt is filtered off and dried, yielding 0.8 parts (16%) of 1-(4-fluorophenylmethyl)-N-{1-[3-(4-methoxyphenylsulfonyl)propyl]-4-piperidinyl}-1H-benzimidazol-2-amine ethanedioate (1:2); mp. 213.1° C.

EXAMPLE LVII

A mixture of 5 parts of ethyl 2-{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy}acetate, 70 parts of ethanamine solution 50% and 40 parts of methanol is stirred for 3 hours at room temperature. The reaction mixture is evaporated and the residue is crystallized twice from 2-propanol, yielding 1 part (19%) of N-ethyl-2-{4-[2-{4-[1-(4-fluorophenylmethyl-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy}acetamide; mp. 160.9° C.

EXAMPLE LVIII

A mixture of 3.5 parts of methyl 2-{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy acetate, 90 parts of concentrated ammonium hydroxide and 40 parts of methanol is stirred for 4 hours at room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanol, yielding 1 part (28.5%) of 2-{4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-phenoxy}acetamide; mp. 180.4° C.

EXAMPLE LIX

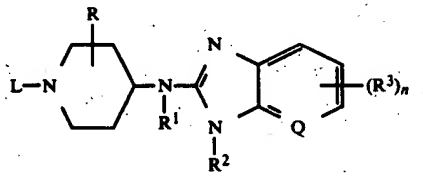
To a stirred and cooled (below 10° C.) mixture of 5.04 parts of carbon disulfide, 2.06 parts of N,N'-methanetetraylbis[cyclohexamine] and 45 parts of tetrahydrofuran is added dropwise a solution of 3.7 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine in tetrahydrofuran. Upon completion, stirring is continued overnight while the mixture is allowed to reach room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 4 parts (100%) of 1-(4-fluorophenylmethyl)-N-[1-(2-isothiocyanatoethyl)-4-piperidinyl]-1H-benzimidazol-2-amine as a residue.

A mixture of 2.1 parts of N-(4-fluorophenylmethyl)-1,2-benzenediamine, 4 parts of 1-(4-fluorophenylmethyl)-N-[1-(2-isothiocyanatoethyl)-4-piperidinyl]-1H-benzimidazol-2-amine and 90 parts of tetrahydrofuran is stirred and refluxed for 2 hours. The reaction mixture is evaporated, yielding 6 parts (100%) of N-{2-[(4-fluorophenylmethyl)amino]phenyl}-N'-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}-ethyl]thiourea as a residue.

A mixture of 6 parts of N-{2-[(4-fluorophenylmethyl-)amino]phenyl}-N'-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]thiourea, 3.2 parts of mercury (II) oxide, 0.1 parts of sulfur. and 90 parts of tetrahydrofuran is stirred and refluxed for 3 hours. The reaction mixture is filtered over Hyflo and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1.2 parts (20%) of 1-(4-fluorophenylmethyl)-N-[1-{2-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]e-thyl}-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 196.9° C.

What is claimed is:

1. A chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of, halo, lower alkyl, lower alkyloxy and trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy,

arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or or an aryl group; 1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula Z-C_mH_{2m}-, wherein

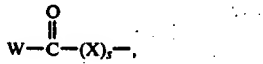
m is an integer of from 1 to 6 inclusive; and

Z is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula T-N(R^4)-, wherein

R^4 is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula



wherein

s is the integer 0 or 1;

X is a member selected from the group consisting of O and —N(R^5)-, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

where aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula R^6—C_pH_{2p}—O—, wherein

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, and a radical of the formula R^7—O—, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-(lower alkyl)aminocarbonyl wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl wherein said aryl is as defined hereabove.

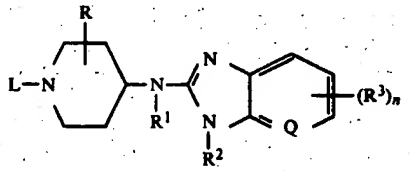
2. A chemical compound selected from the group consisting of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine and the pharmaceutically acceptable acid addition salts thereof.

3. A chemical compound selected from the group consisting of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol and the pharmaceutically acceptable acid addition salts thereof.

4. A chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}-benzeneacetate and the pharmaceutically acceptable acid addition salts thereof.

5. A chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy}acetonitrile and the pharmaceutically acceptable acid addition salts thereof.

6. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



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and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy, trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryl-

lower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula $Z\text{-}C_mH_{2m}$—, wherein

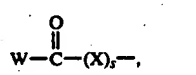
m is an integer of from 1 to 6 inclusive; and

Z is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula T-N(R^4)-, wherein

R^4 is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2yl; and

a radical of the formula



wherein

s is the integer 0 or 1;

X is a member selected from the group consisting of O and -N(R^5)-, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl-)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6\text{—}C_pH_{2p}\text{—}O$—, wherein

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula R^7-O-, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-(lower alkyl)aminocarbonyl, wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl wherein said aryl is as defined hereabove.

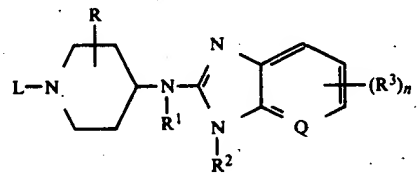
7. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine and the pharmaceutically acceptable acid addition salts thereof.

8. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenol and the pharmaceutically acceptable acid addition salts thereof.

9. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl}benzeneacetate and the pharmaceutically acceptable acid addition salts thereof.

10. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy}acetonitrile and the pharmaceutically acceptable acid addition salts thereof.

11. A method to prevent the release of histamine in warm-blooded animals, which comprises the systemic administration to said animals of an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy, trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula $Z\text{-}C_mH_{2m}$-, wherein

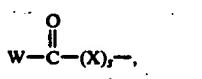
m is an integer of from 1 to 6 inclusive; and

Z is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula $T\text{-}N(R^4)$-, wherein

R^4 is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula



wherein

s is the integer 0 or 1;

X is a member selected from the group consisting of O and $-N(R^5)$—, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6\text{—}C_pH_{2p}\text{-O—}$, wherein

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula $R^7\text{-O—}$, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl,

wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl wherein said aryl is as defined hereabove.

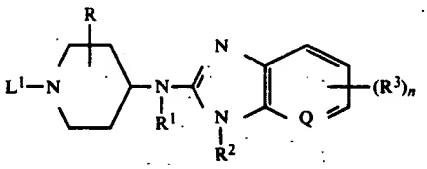
12. A method to prevent the release of histamine in warm-blooded animals, which comprises the systemic administration to said animals of an effective antihistaminic amount of a chemical compound selected from the group consisting of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine and the pharmaceutically acceptable acid addition salts thereof.

13. A method to prevent the release of histamine in warm-blooded animals, which comprises the systemic administration to said animals of an effective antihistaminic amount of a chemical compound selected from the group consisting of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}-ethyl]phenol and the pharmaceutically acceptable acid addition salts thereof.

14. A method to prevent the release of histamine in warm-blooded animals, which comprises the systemic administration to said animals of an effective antihistaminic amount of a chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-phenyl}benzeneacetate and the pharmaceutically acceptable acid addition salts thereof.

15. A method to prevent the release of histamine in warm-blooded animals, which comprises the systemic administration to said animals of an effective antihistaminic amount of a chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]-phenoxy}acetonitrile and the pharmaceutically acceptable acid addition salts thereof.

16. A chemical compound having the formula



wherein:

L^1 is a member selected from the group consisting of hydrogen, lower alkyloxycarbonyl and phenylmethoxycarbonyl;

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of, halo, lower alkyl, lower alkyloxy, trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)-thienyl, pyridinyl, mono- and di(lower alkyloxy)-pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substitued phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyl-lower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6—C_pH_{2p}—O—$, wherein

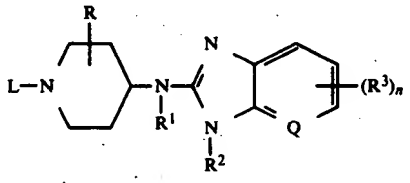
p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula R^7-O-, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl and phenylcarbonyl, wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy.

17. A chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl;

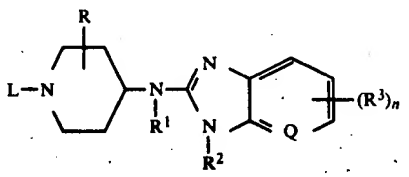
n is an integer of from 0 to 2 inclusive; Q is a member selected from the group consisting of CH and N; and L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; and aryllower alkenyl; wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6—C_pH_{2p}—O—$, wherein

p is an integer of from 1 to 6 inclusive; and R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, and

a radical of the formula $R^7—O—$, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-(lower alkyl)aminocarbonyl, wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy.

18. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy, trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl and aryllower alkenyl; wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6—C_pH_{2p}—O—$, wherein

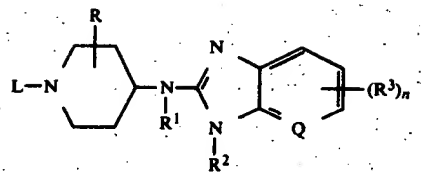
p is an integer of from 1 to 6 inclusive; and R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula $R^7—O—$, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-(lower alkyl)aminocarbonyl,

wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy.

19. A method to prevent the release of histamine in warm-blooded animals, which comprises the systemic administration to said animals of an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy, trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6—C_pH$ ..... 2p—O—, wherein

p is an integer of from 1 to 6 inclusive; and R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula $R^7—O—$, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-(lower alkyl)aminocarbonyl, wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy.

* * * * *

EXHIBIT B

April 28, 1981

REC'D IN MAIL DIV.
U.S. PATENT OFFICE

The Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Re: U.S. Patent No. 4,219,559
Serial No. 2,276
Our File JAB 286

Dear Sir:

Our records indicate that the above-identified patent, as issued, contains the following errors:

Claim 1, line 55, insert the word "selected" after the word "member".

Claim 12, line 15, "is" should be -- in --.

Claim 19, line 46, omit the dots after "H" -- formula should read "R^0 C_pH_{2p}-O-."

Please make proper record in the above-identified patent application.

Very truly yours,

Geoffrey G. Dellenbaugh
Attorney for Assignee
Reg. No. 26,864

GGD/dls
501 George Street
New Brunswick, N.J. 08903
(201) 524-9324

EXPRESS MAIL # MB132880341
Date of Deposit - 2/10/89

EXHIBIT C

Astemizole IND: Summary of Activity

April 22, 1980	FDA received IND for Astemizole as a histamine H_1-antagonist IND # 17,431 assigned	_____
May 23, 1980 Phone	IND on clinical hold. A letter outlining FDA's questions is forthcoming	_____
May 27, 1980	Submitted part 16 of IND (GLP statements) which was inadvertently omitted from our original submission	_____
June 11, 1980 Letter from FDA	Letter outlining FDA's requests concerning the clinical hold status of the IND	Answered 8/08/80
October 31, 1980	Effective date of IND # 17,431	_____
November 14, 1980 Letter from FDA	Request for comparative pharmacokinetic data from lab animals and man as well as a Segment I reproduction study	Answered in part 12/11/80 Answered 4/10/81
March 6, 1981 Letter from FDA	FDA reviewed protocols 002/003 in 12/11/80 amendment, and requests more information be submitted within 60 days of the issuance of this letter	Answered 4/10/81
May 1, 1981 Letter from FDA	FDA's review of 12/11/80 amendment is complete. The proposed Phase I study can begin. All other studies with a possible dosing duration of more than 30 days should be withheld until comparative pharmacokinetic data are generated. Women of childbearing potential should not be included. Submit background data on abnormalities of such a type as already encountered in previous experiments in Segment I reproduction studies.	Answered in part 6/10/81 Answered 8/31/81

Astemizole IND: Summary of Activity

May 15, 1981	Progress report	_____
July 13, 1981 Letter from FDA	FDA reviewed our amendment of 6/10/81 and requested that the proposed clinical studies with possible daily administration of astemizole for one year should not be initiated at this time. The steady state levels and/or possible accumulation of drug should be studied in dogs following repetitive daily dosing.	_____
August 17, 1981 Letter from FDA	FDA completed review of amendments dated 3/27/81, 4/10/81, 4/13/81, 5/5/81 and 7/9/81 (protocols 004, 005 and revisions). FDA does not feel women of child bearing potential should be in studies. Request comparative pharmacokinetic data in animals and man and Segment I reproduction studies. FDA does not concur with the inclusion of 12-17 yr. olds in studies. Segment III reproduction studies should be performed.	_____
August 19, 1981 Phone	FDA said that any 17 year olds that are already in studies can remain in the studies thru both the double-blind and long-term periods. Treatment of all children under 17 now enrolled in studies must stop. All patients entered in future must be 18 or above. FDA is concerned about the unusual pharmacokinetics and safety of drug.	Confirmed 8/28/81

Astemizole IND: Summary of Activity

September 9, 1981 Letter from FDA	No women of child-bearing potential may be entered into any new or ongoing studies. No children under the age of 18 may be admitted to any studies.	Answered 9/24/81
September 10, 1981	Submission of revised Investigators Brochure.	_____
November 9, 1981 Letter from FDA	FDA letter clarifying several telephone conversations between Janssen, FDA and Dr. Brobyn regarding the status of using astemizole for compassionate clearance cases. Letter outlines criteria that must be met for patients to receive astemizole on a humanitarian basis.	_____
November 11, 1981 Letter from FDA	FDA requests we institute more thorough screening procedures prior to the initiation of clinical studies. No subjects with a history of depression should be admitted to clinical trials of astemizole.	Answered 12/18/81
December 15, 1981 Letter from FDA	FDA's comments and requests concerning our amendments of 8/31/81 and 9/10/81: Plasma levels following single and multiple dosing of astemizole in dogs should be determined. Investigator's brochure should be amended to include adverse effects observed in toxicity study in dogs. Meeting should be arranged with FDA.	Answered 2/4/82
February 2, 1982 Letter from FDA	FDA requests we provide the dosages in mg/kg for the rat Segment I and Segment III reproduction studies referred to in our 8/31/81 amendment.	Answered 4/7/82
December 29, 1981	Submission of preliminary results on decay levels of astemizole and its hydroxylated metabolites in plasma samples taken from Dr. Brobyn's patients.	_____

Astemizole IND: Summary of Activity

June 11, 1982 Letter from FDA	The Division of Biopharmaceutics has reviewed our amendment dated 12/29/81 and requested that we should determine the pharmacokinetics of both the parent drug and the major metabolite(s) separately. The determined drug plus metabolite plasma levels and elimination half-life are misleading.	_____
September 8, 1982 Phone	Shvartzman, FDA, called to request that we make a listing of all our clinical studies with the total number of patients enrolled.	Answered 9/10/82
September 24, 1982 Letter from FDA	FDA completed review of amendments of 6/11 and 2/9/82 and have several comments and requests which require a response.	Answered 12/03/82
October 8, 1982 Meeting	Minutes of 10/6/82 meeting with FDA. Discussions included Pharmacokinetics; Safety; Dosing; Clinical; Bioavailability. Actions needed and responsibility were decided upon.	Answered 1/4/83
January 14, 1983 Letter from FDA	FDA's comments concerning additional clinical and preclinical trials as a result of the November 4, 1982 Pulmonary-Allergy Drugs Advisory Committee Meeting.	Answered in part 2/11/83 Answered 3/25/83 and 11/23/83
February 10, 1983 Letter from FDA	End-of-Phase II letter.	_____
March 16, 1983	Submission of reports available to date on the pharmacology of astemizole.	_____

Astemizole IND: Summary of Activity

March 31, 1983 Letter from FDA	FDA completed review of our 2/11/83 amendment (Protocol 025) and have several comments. The design of this study needs to be improved.	_____
June 8, 1983 Letter from FDA	FDA's review and comment of our 1/4/83 amendment. Request we provide complete documentation for each analytical method used in study. Every attempt should be made to use specific RIA procedure, submit all data analyzed.	_____
June 22, 1983 Meeting	Discussion of the seasonal rhinitis protocol for astemizole. This protocol allows for the inclusion of women of child-bearing age, who are currently on oral contraceptives or who utilize IUD's.	_____
August 9, 1983	FDA received IND for Astemizole in vertigo. IND # 22,560 assigned	_____
August 30, 1983	FDA received IND for astemizole in urticaria. IND # 22,676 assigned	_____
November 18, 1983 Letter from FDA	Request for clinical study on spermatogenesis.	Protocol submitted 7/19/84, revised 8/20/84, in response to 7/26/84 meeting. Report submitted 7/25/86.
January 23, 1984	Letter to FDA requesting pre-NDA meeting to discuss the drug and our plans for an NDA. We will submit for review prior to such meeting a pre-NDA dossier.	_____
February 10, 1984	Submission of two-volume dossier for review by FDA in preparation for pre-NDA meeting.	_____
March 12, 1984 Meeting	Pre-NDA meeting	Minutes 5/25/84

Astemizole IND: Summary of Activity

March 22, 1984 Letter from FDA	FDA has reviewed amendments 2/4/82, 10/6/82, 3/25/83, 11/23/83 and 2/2/84 and have comments and recommendations concerning spermatogenesis.	Answered 5/31/84
April 18, 1984 Meeting	Meeting with P. Russell (FDA) regarding the premature nature of requesting long-term studies.	_____
May 4, 1984	Report entitled "Oral Carcinogenicity Study in Albino Swiss Mice."	_____
May 11, 1984	Request for submission of toxicity studies.	Submitted 6/11/84
August 6, 1984 Letter from FDA	Comments regarding assay methods used in dog study to determine tissue levels and elimination rate of astemizole.	_____

HISMANAL NDA Studies

Seasonal Rhinitis

Investigator	Country	Number of Patients by Treatment Group			
		Astemizole	Placebo	Terfenadine	Other[1]
*Bernstein/030	USA	30	30	-	-
*Bernstein/022	USA	45	15	-	-
*Honsinger/026	USA	25	25	-	-
*Middleton/023	USA	32	10	-	-
*NJ Multicenter	USA	51	52	-	-
*Townley/031	USA	30	30	-	-
*Cortella	Argentina	16	16	-	-
Novotny	Austria	30	-	-	30
*Clarysse	Belgium	47	48	-	-
*LeClerq	Belgium	49	-	-	51
*Pattyn	Belgium	80	-	-	44
**Knight/Rhinitis	Canada	46	34	-	-
*Malmberg	Finland	16	15	-	20
*Garcelon	France	14	-	-	15
*Olzem	Germany	30	-	-	33
*O'Donnell	New Zealand	7	8	-	-
*Wilson/010	New Zealand	16	16	-	-
*Frostad	Norway	18	-	-	23
*Botha	South Africa	27	29	-	-
*Moller	Sweden	40	-	-	20
*Lofkvist	Sweden	25	-	-	26
*Gilliet	Switzerland	22	-	24	-
*Schmid	Switzerland	15	-	-	17

[1]Other includes: Chlorpheniramine, clemastine, sodium cromoglycate, mequitazine, ketotifen or pheniramine maleate

*Indicates a double-blind study

**Study had both a double-blind and an open label phase

HISMANAL NDA Studies

Seasonal Rhinitis

Investigator	Country	Number of Patients by Treatment Group			
		Astemizole	Placebo	Terfenadine	Other[1]
*Batchelor	UK	53	52	-	-
*D'Souza	UK	17	18	-	-
Flowers	UK	9	-	-	10
**Hammond	UK	80(45)	88	-	-
*Hedley	UK	47	50	-	-
*Howarth/502	UK	32	31	-	-
*Howarth/130	UK	30	28	32	-
Wood/131	UK	42	-	43	-
Wood/103	UK	26	-	-	27

Perennial Rhinitis

*Bierman/005	USA	40	20	-	-
**Brobyn/004	USA	59	20	-	-
Brobyn/020	USA	10	-	-	-
**Brobyn/004D	USA	23	8	-	-
**Caldwell/003	USA	51	18	-	-
*Wilson/014	USA	58	27	-	28
*Callier	Belgium	45	46	-	-
*Chalmagne	Belgium	22	-	-	18
*DeGreef	Benelux	22	-	-	22
*Nuchel-Peterson	Denmark	55	27	-	-
Wihl	Sweden	5	-	-	-
*Sibbald	UK	22	21	-	-

[1]Other includes: Chlorpheniramine, clemastine, sodium cromoglycate, mequitazine, ketotifen or pheniramine maleate

*Indicates a double-blind study

**Study had both a double-blind and an open label phase

HISMANAL NDA Studies

Urticaria

Investigator	Country	Number of Patients by Treatment Group: Astemizole	Placebo	Terfenadine	Other[1]
**Bernstein/028	USA	38	27	-	-
**Fox/033	USA	44	26	-	-
**Knight/Urticaria	Canada	31	17	-	-
* Damseaux	Belgium	35	35	-	-

Vertigo

Turner/Jackson	USA	11	-	-	-

Conjunctivitis

Geria	Argentina	12	-	-	-
*DeClerq	Belgium	25	27	-	-
*Lods	France	20	-	-	20

Seasonal Allergic Conjunctivitis

**Sobocki	Sweden	19(38)	19	-	-

Asthma

P. DeBode	Belgium	10	-	-	-
DeBrabandere	Belgium	29	-	-	-
*Samanek	Czechoslovokia	15	15	-	-
*M. Samanek	Czechoslovokia	15	15	-	-
*Prinsen	Netherlands	17	-	-	19

[1]Other includes: Chlorpheniramine, clemastine, sodium cromoglycate, mequitazine, ketotifen or pheniramine maleate

*Indicates a double-blind study

**Study had both a double-blind and an open label phase

HISMANAL NDA Studies

Bronchitis

Investigator	Country	Astemizole	Number of Patients by Treatment Group Placebo	Terfenadine	Other[1]
*DeLoore	Belgium	12	11	-	-

Multiple Indications

*T. Callier	Belgium	26	19	-	-
DeCree	Belgium	38	-	-	-
Stevens	Belgium	38	-	-	-
Verhaegen	Belgium	19	-	-	-

[1]Other includes: Chlorpheniramine, clemastine, sodium cromoglycate, mequitazine, ketotifen or pheniramine maleate

*Indicates a double-blind study

**Study had both a double-blind and an open label phase

Hismanal NDA: Summary of Activity

November 26, 1984	Date of receipt by FDA of manufacturing and controls section of the NDA for astemizole	_____
February 25, 1985	Date of receipt by FDA of full NDA for Astemizole. NDA # 19-402 assigned to Astemizole	_____
February 19, 1985 Letter from FDA	Manufacturing and controls deficiencies	Answered in part 10/10/85 and completed 6/19/86
May 20, 1985	Submission of patent information	_____
May 30, 1985 Phone	Request from Dr. Tai, Biopharmaceutics reviewer concerning validation of R.I.A. procedure	Answered in part 6/03/85 (phone) and completely 6/13/85
June 26, 1985 Meeting with FDA	Discussion concerning biopharmaceutics and toxicology sections of the NDA	_____
August 21, 1985 Phone	FDA request for repeat carcinogenicity study	Meeting 9/10/85 Answered 9/30/85 (Review clock extended 120 days)
October 3, 1985 Letter from FDA	Bioavailability/Dose Proportionality deficiencies	Answered in part 10/24/85 and completely 2/14/86 (60 day clock extension)
November 19, 1985 Phone	Reports on four overseas adverse reactions	_____
December 18, 1985 Phone	Request from Dr. Huang, Biometrics Division, for additional calculations of efficacy data	
January 18, 1986 Letter from FDA	Manufacturing and controls requests (6/18/86 request for clarification)	Answered 6/19/86 (60 day clock extension)
March 28, 1986 Phone	Request from FDA for clarification of minor chemistry questions	Answered 6/19/86

Hismanal NDA: Summary of Activity

May 29, 1986 June 5, 1986 Meetings with FDA	Meetings on status of NDA	_____
June 19, 1986 Letter from FDA	Request for a repeat 24 month carcinogenicity study	Answered 7/08/86 (90 day day clock extension)
June 19, 1986 Letter from FDA	Comments and requests on statistical analysis of clinical data	Answered 7/14/86 (60 day clock extension)
July 16, 1986 Phone	Requests from FDA concerning various chemistry issues	Answered 7/30/86
July 25, 1986	Submission of spermatogenesis study in response to IND commitment	(90 day clock extension)
August 20, 1986 Phone	Request from Dr. Tai for information concerning dissolution data	Answered 8/27/86
September 18, 1986	Request for tabulation of sedation related adverse reactions	Answered 9/26/86
September 25, 1986 Letter from FDA	Request for change in dissolution specification	Phone call with FDA 10/6/86 Answered 10/9/86
October 14, 1986 Letter from FDA	Request for commitments on Phase IV bioavailability study and labeling revisions and submission of samples	Answered 11/5/86 Samples submitted 11/21/86
October 28, 1986 Phone	Request for rationale for 10 mg dose	Answered 12/4/86
November 7, 1986	Biometrics reviewer requested additional tables on analysis of carcinogenicity study	Conference call 11/10/86 Answered 12/4/86

Hismanal NDA: Summary of Activity

November 7, 1986	Submission of methods validation package	_____
November 26, 1986	Biometrics reviewer requested peto analysis for the carcinogenicity study.	Answered 12/4/86
December 17, 1986 Letter from FDA	Requests pertaining to Biopharmaceutics review	Answered 1/6/87
January 6, 1987 Meeting	Biometrics review of repeat 24 month carcinogenicity study completed	_____
January 28, 1987 Meeting	Review of repeat carcinogenicity study completed. Pharmacology review completed. No outstanding issues. Approvable.	_____
January 28, 1987 Meeting	Biometrics review of 7/17/86 safety and efficacy responses and 7/25/86 spermatogenesis study completed.	_____
February 17, 1987 Phone	Chemistry and Biopharmaceutics reviews completed. No outstanding issues. Approvable.	
February 19, 1987 Phone	FDA request for samples for methods validation	Samples submitted 2/25/87
February 20, 1987 Letter from FDA	Comments and requests from Biometrics 7/14/86 and 7/25/86 submissions	Meeting 3/5/87. Answered 3/30/87 (60 day clock extension).
March 10, 1987 Phone	Requests from FDA laboratories on methods validation	Answered 3/13/87
March 17, 1987 Phone	FDA recommendation that submission of revised labeling would be helpful	Submitted 05/01/87 (60 day clock extension)
April 7, 1987	Safety update submitted	_____

Hismanal NDA: Summary of Activity

April 13, 1987 Phone	Request from Biometrics for data tabulations and floppy disks	Submitted 4/17/87
April 20, 1987	Environmental assessment submitted	_____
May 11, 1987 Letter from FDA	Request for reformatted environmental assessemnt	Meeting 5/15/87 Submitted 6/08/87
June 12, 1987 Meeting	Request from FDA laboratories for commitment to revise validation procedures	Submitted 6/15/87
June 17, 1987	Response to all outstanding mfg/controls issues: (dissolution, HPLC assay, degradants and inclusion of empirical formula in package insert).	_____
June 26, 1987 Meeting	Tabulation of patients who reported "sedation" requested by medical reviewer	Submitted 6/26/87
June 26, 1987 - July 31, 1987 Phone	Ongoing discussions with Biometrics and Surgical-Dental Divisions to obtain resolution on Biometrics review.	_____
July 31, 1987	Review of methods validation completed. No outstanding issues. Approvable.	_____
July 31, 1987	Biometrics review completed. No outstanding issues.	_____
August 20, 1987	Primary medical review completed	_____
September 11, 1987	Medical review completed by Division Director	_____

Hismanal NDA: Summary of Activity

September 29, 1987	Revised primary medical review completed, incorporating comments by Division Director	_____
December 14, 1987	Review of medical summary and package insert by supervisory medical officer completed	_____
December 18, 1987	Review of medical summary summary and package insert completed by Division Director	_____
January 11, 1988	Surgical-Dental Division met to review draft labeling; no major issues	_____
January 26, 1988	Revised medical review, incorporating comments from 1/11/88 meeting completed	_____
February 2, 1988	Primary and secondary reviews of NDA approvable package completed. SBA should be available immediately upon request	_____
February 10, 1988 Phone	Request from medical reviewer for sub-mission of all cardio-vascular adverse reactions reported for astemizole patients	Submitted 2/16/88
February 23, 1988	NDA approvable package sent to ODER	_____
March 1, 1988	Reviews by Dr. Kumkumian and Dr. Glocklin completed; approvable package sent to Dr. Botstein. Dr. Botstein requested SBA and had minor questions which were answered by phone.	Draft SBA submitted 03/04/87

Hismanal NDA: Summary of Activity

March 7, 1988	Dr. Walters and Ms. Linda Carter stated that Dr. Botstein is actively reviewing NDA package	_____
March 30, 1988	Dr. Botstein indicated that she is working toward completion of her review	_____
April 4, 1988 Phone	Request for revisions to pharmacology/toxicology section of SBA	Submitted 4/10/88
April 11, 1988- May 18, 1988	Labeling under review by Surgical-Dental Division and Dr. Botstein.	_____
May 31, 1988 Meeting	In response to the "midazolam" hearings, Dr. Walters requested that we submit information on non-U.S. vs. U.S. labeling	Submitted 6/22/88
June 23, 1988 Meeting	Dr. Walters indicated that follow-up safety update should be submitted	Submitted 6/28/88
July 22, 1988 Phone	Request for additional information pertaining to 6/22/88 non-U.S. labeling submission and 6/28/88 follow-up safety update	Submitted 7/25/88
July 27, 1988	Ms. Linda Carter, Special Assistant to Dr. Botstein, stated that Dr. Botstein is actively reviewing the NDA package	_____
August 19, 1988 Phone	Request for information on rejection of astemizole application in Norway	Meeting 9/4/88 Answered 9/6/88
October 7, 1988	Approvable letter with requests for information	Answered in part 10/17/88 Meeting 10/28/88 Answered 11/07/88

Hismanal NDA: Summary of Activity

October 31, 1988	Request for more information on depressed patients	Answered 11/07/88
December 1, 1988 Phone	Requests for information concerning 11/7/88 submission	Answered 12/7/88
December 7, 1988 Phone	Request for information concerning dissolution and hardness data submitted on 12/7/88	Answered 12/8/88 (Review clock extended 60 days)
December 15, 1988 Letter from FDA	Draft labeling with a request for a revised package insert in accordance with this draft	Answered in part 12/16/88 Meeting 12/22/88; Answered 12/22/88
December 29, 1988 Letter from FDA	NDA Approval	Submitted final printed labeling and draft promotional material for launch 12/29/88

EXHIBIT D

JAB 286

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Frans Janssens, Raymond Stokbroekx, Joseph Torremans and Marcel Luyckx

U.S. Patent No.: 4,219,559

Issued: August 26, 1980

For: N-HETEROCYCLYL-4-PIPERIDINAMINES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

CERTIFICATION

I hereby certify that this Application for Extension of Patent Term Under 35 U.S.C. 156 as well as all Exhibits A through E thereto is being submitted in duplicate to the Commissioner of Patents and Trademarks, Box Patent EXT, Washington, D.C. 20231

Date: February 10, 1989

David J. Levy
Registration No. 27,655
Attorney for Applicants

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(201) 524-2821
February 10, 1989

STATE OF NEW JERSEY)
ss.
COUNTY OF MIDDLESEX

BE IT REMEMBERED, that on this 10th day of February, 1989, before me, a Notary Public, personally appeared David J. Levy, who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the contents thereof, he did acknowledte that he signed, sealed, and delivered the same and his voluntary act and deed for the uses and purposed therein expressed.

Notary Public

RUTH ANN KREIGER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires October 10, 1989

EXPRESS MAIL # MB132880341
Date of Deposit - 2/10/89

EXHIBIT E

JAB 286

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Frans Janssens, Raymond Stokbroekx, Joseph Torremans and Marcel Luyckx

U.S. Patent No.: 4,219,559

Issued: August 26, 1980

For: N-HETEROCYCLYL-4-PIPERIDINAMINES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

DECLARATION

Dear Sir:

I, DAVID J. LEVY, residing at 22 Highmont Drive, West Windsor, New Jersey 08691 , declare as follows:

1) THAT I am a Patent Attorney authorized to practice before the United States Patent and Trademark Office (registration number 27,655) and have general authority to act in patent matters on behalf of Janssen Pharmaceutica N.V., the owner of the above-identified patent for which term extension is being requested.

2) THAT I have reviewed and understand the content of the application for patent term extension which is submitted pursuant to 35 U.S.C. 156 of which the present Declaration is attached as Exhibit D.

3) THAT I believe that U.S. Patent 4,219,559 is subject to extension pursuant to 37 C.F.R. 1.710.

4) THAT I believe an extension of two years of the term of U.S. Patent 4,219,559 is justified under 35 U.S.C. 156 and the applicable regulations.

EXPRESS MAIL # MB 132880341
Date of Deposit - 2/10/89

5) THAT I believe U.S. Patent 4,219,559 for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I hereby declare that all statements made herein of my own knowledge are believed true and tht all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so make are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent 4,219,559.

Date: February 10, 1989 David J. Levy

STATE OF NEW JERSEY)

ss.

COUNTY OF MIDDLESEX

BE IT REMEMBERED, that on this 10th day of February, 1989, before me, a Notary Public, personally appeared David J. Levy, who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the contents thereof, he did acknowledte that he signed, sealed, and delivered the same and his voluntary act and deed for the uses and purposed therein expressed.

Notary Public

RUTH ANN KREIGER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires October 10, 1989